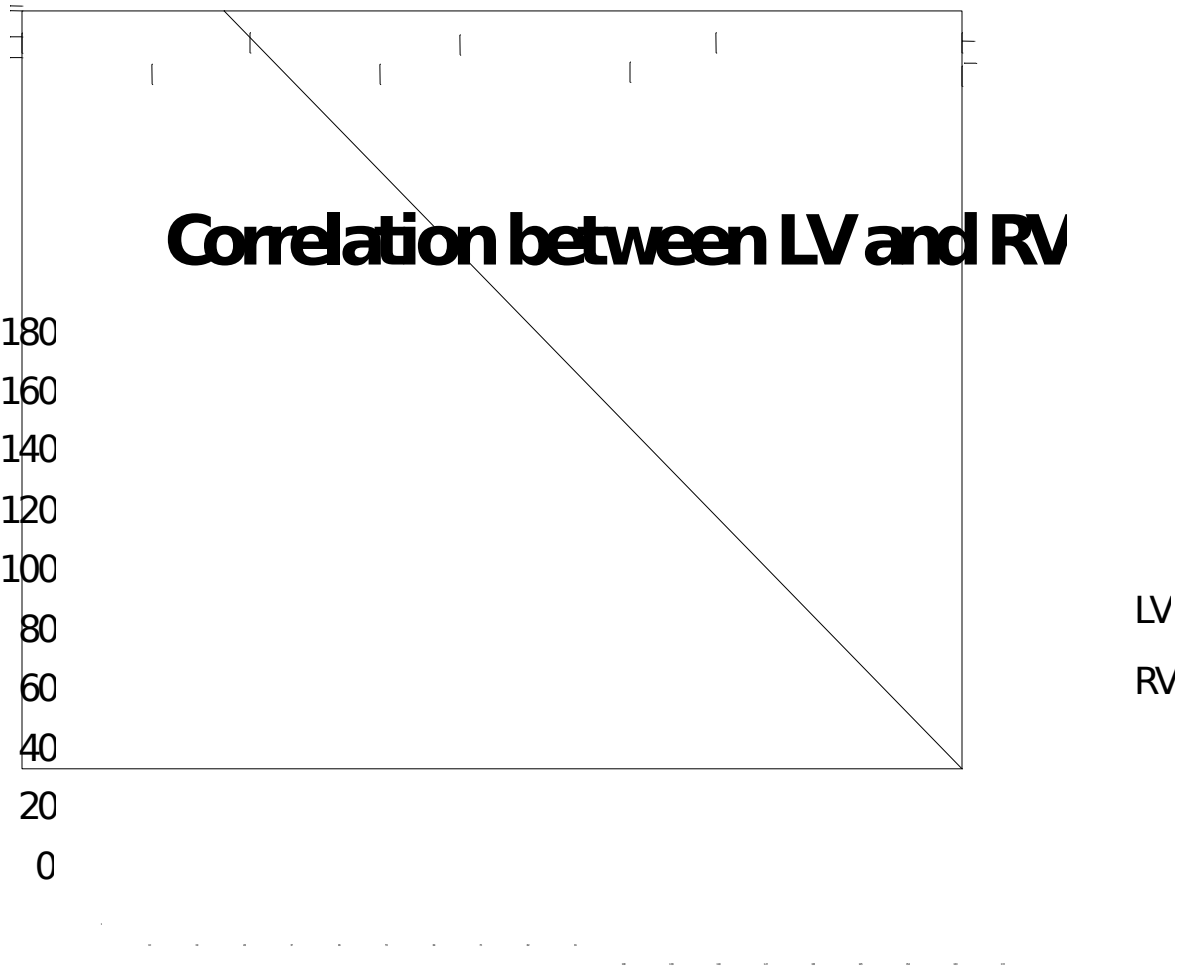


correlation between LV and RV for control group

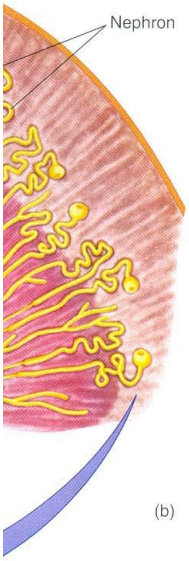
Chapter one
Introduction

(1.1) Anatomy physiology and Pathophysiology of the Kidney

(1.1.1) Renal Anatomy

(1.1.1.1) macroscopic structure of the kidney:

T he kidneys are paired organ lying at the posterior wall of the abdominal cavity just above the waistline, at about the level of the 12th rib. Each kidney is roughly bear shaped and is about the size of fist. Although most abdominal organs are enclosed within the peritoneum, a clear membrane that lines the abdominal cavity, the kidneys are located between the peritoneum and the walls of the abdominal cavity. Each kidney weights only (115-170 gram) (less than half a pound), their combined weights is less than 1% of the body weight of an average adult **.** Despite their small fraction of body weight, the kidneys received about 20% of the cardiac output under normal resting conditions. This rich blood supply is critical to the kidneys function not only because it provides them with oxygen and nutrients, but also because it enables the kidney to remove or to clear unneeded solutes and water from the body at a rapid rate and eliminates them as urine. The kidneys receive their blood supply from the renal arteries which branch off the aorta and enter each kidney at a region called the renal hilus. The blood returns to the general circulation via the renal veins, which runs parallel to the renal arteries and drain into the infection vena cava (Figure1.1) (William J,2005)



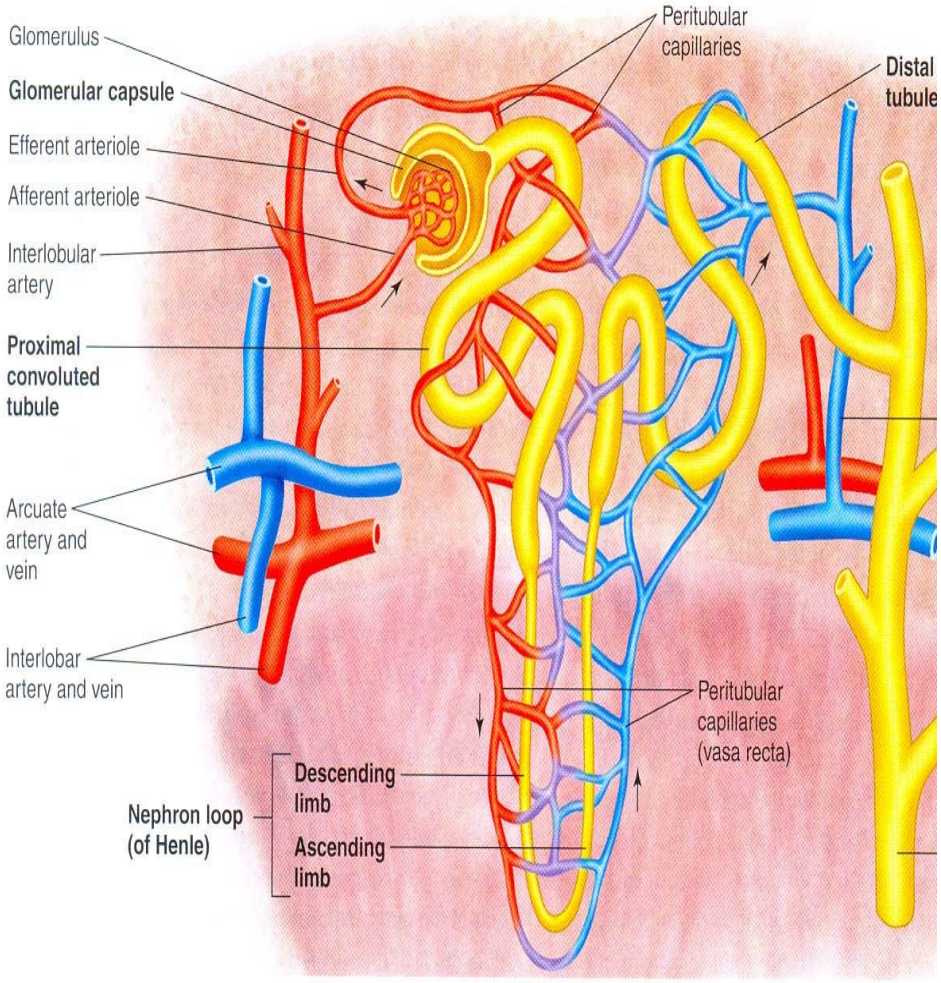
(Figure1.1): Macroscopic structure of the kidney (Stuart,2006)

(1.1.1.2) Microscopic structure of the kidney:

The nephron is the functional unit of the kidney responsible for the formation of urine. Each kidney contains more than a million nephrons. A nephron consists of glomeruler capsule, proximal convoluted tubules, descending limb of the loope of Henle, ascending loope of Henle and distal convoluted tubules. The glomerular capsule surrounds the glomerulus and they are both located in the cortex of the kidney. The capsule contains an inner visceral layer of epithelium around the glomerular capillaries and an outer parietal layer. The space between these two layers is continuous with the lumen of the tubules and receives the glomerular filtrate, and then it passes into the lumen of the proximal convoluted tubules. The walls of the proximal convoluted tubules consist of the single layer of cuboid cells containing millions of microvilli; these microvilli increase the surface area of reabsorption. Salts, water and other molecules needed by the body are transported

from the lumen, though the tubular cells and into the surrounding peritubular capillaries. Fluid passes from the proximal convoluted tubules to the loop of Henle. This fluid is carried into the medulla in the descending limb of the loop of Henle and return to the cortex in the ascending limb of the loope of Henle. Back in the cortex, the tubule becomes coiled and is called distal convoluted tubules. The distal convoluted tubule is shorten than the proximal convoluted tubules and relatively has few microvilli. The distal convoluted tubules terminates as it empties into a collecting duct. The collecting duct receives fluid from the distal convoluted tubules of several nephrons.

Fluid is then drained by the collecting duct from the cortex to the medulla as the collecting duct passes through the renal pyramids. This fluid now called urine passes into the major calyx. Urine is then funneled through the renal pelvis and out of the kidney in the ureter. (Figure1.2) (Stauart,2006)



(Figure1.2): microscopic structure of the kidney (Stuart,2006)

(1.1.1.3)Renal blood vessels:

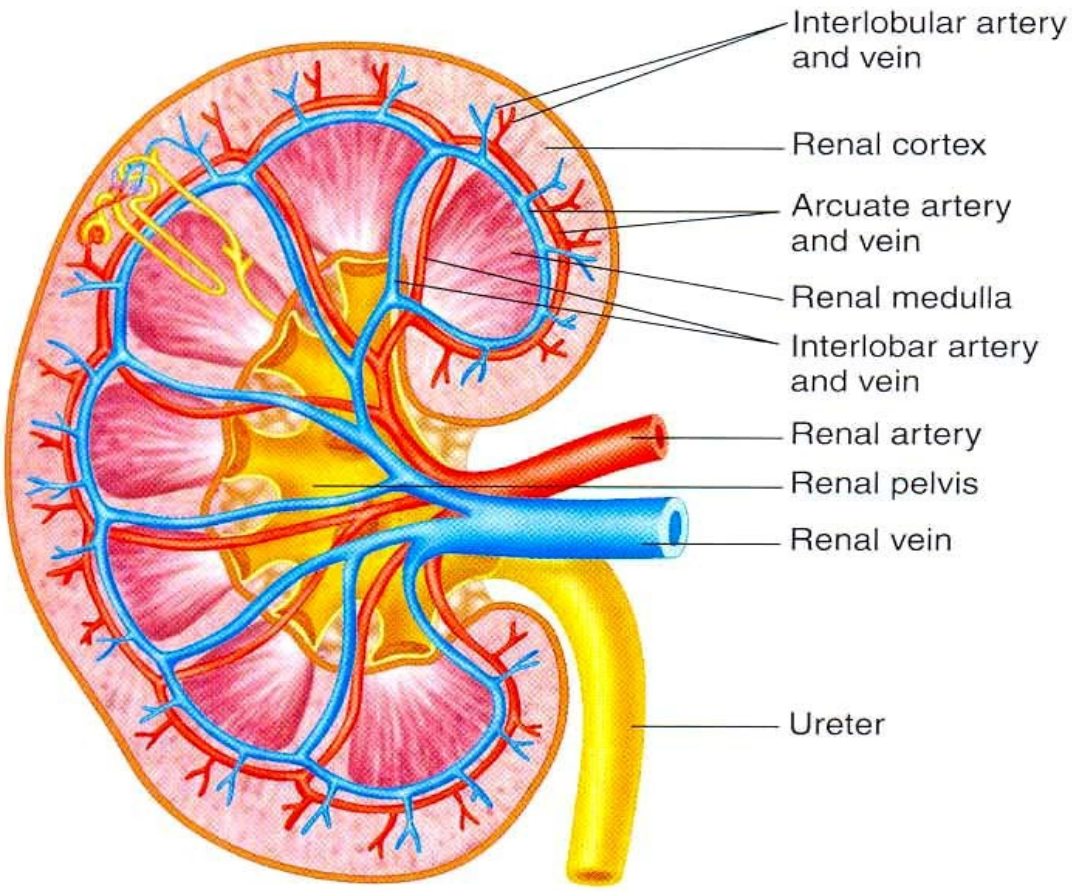
The kidneys are supplied by oxygenated blood through renal arteries. Renal artery arises from the abdominal aorta immediately below the superior mesenteric artery (SMA) and then it directed across the crus of diaphragm and form right angle to the aorta. There maybe

one or more renal arteries supply each kidney. When the renal artery enters the kidney it located above the renal vein. It has a radius of approximately 0.25cm at the root. The measured mean diameter can differ depending on the image method used, for example the diameter was found to be (5.04 ± 0.7) using ultrasound, but (5.68±1.19) using angiography . Due to the position of aorta, the inferior vena cava (IVC) and the kidney in the body, the right renal artery is normally longer than the left renal artery. The right passes behind the (IVC), the right renal vein, the head of pancreas and the descending part of the duodenum. The left renal artery is somewhat higher than the right; it lies behind the left renal vein, the body of pancreas and the splenic vein, and is crossing by the inferior mesenteric vein.

Arterial blood inters the kidney through renal artery, which divided into interlobar artery that passes between pyramids through the renal columns. Arcuate arteries branch from the interlobar arteries at the boundary of the cortex and medulla. A number of interlobular arteries radiate from the arcuate arteries into the cortex and subdivided into numerous afferent arterioles which are microscopic. The afferent arterioles deliver blood into glomeruli capillary networks that produce a blood filtrate that enter the urinary tubules. The blood remaining in the glomerulus leaves through an efferent arteriole, which deliver the blood into another capillary network- the peritubular capillaries surroundings the renal tubules.(Elaine N,2003)

This arrangement of blood vessel is unique, it is the only one of the body in which a capillary bed (glomerulus) is drained by an arteriole rather than by a venule and delivered to a second capillary bed located downstream (the peritubular capillaries). Blood from peritubular capillaries drain into veins that parallel the course of the arteries in the kidney. These veins are called interlobular, arcuate and interlobar veins. The interlobar veins descend between the pyramids, converge and leave the kidneys as a single renal vein, which empties into the inferior vena cava. (Figure1.3) (Boron,2005).

Renal blood flow (RBF) is the volume of blood delivered to the kidneys per unit time. In humans, the kidneys together receive roughly 25% of cardiac output, amounting to 1.5 liter per minute in a 70 kg adult male. Renal blood plasma (RBP) is the volume of blood plasma delivered to the kidney per unit time. While the two terms (RBF) and (RBP) generally apply to arterial blood delivered to the kidney, both (RBF) and (RBP) can be used to quantity the volume of the venus blood existing the kidney per unit time. (Stauart,2006)


Interlobular artery and vein
Renal cortex
Arcuate artery and vein
Renal medulla
Interlobar artery and vein
Renal artery
Renal pelvis
Renal vein
Ureter

(Figure1-3): Renal blood vessels (Gerhard,1985)

(1.1.1.4) Normal renal size:

The development or increase in the size of the kidney stops at the age of 25 or 26. when the kidney stop to increase in size, the average length usually reach 12cm while the width is approximately 6cm. The mean thickness of kidney is around 3cm. With these dimensions, any decrease in the kidney size in abnormal. However the size of the kidney can still grow after maturation. This can happen if one of the kidneys was removed. The remaining kidney increases to compensate the functions of the other kidney ((Gerhard,1985) .

The normal size of the kidney in the human is fist size. There are same factors that can affect the abnormal growth in size. One of the factors is the development of a cyst in the kidney. When cyst starts to develop, the kidney can grow as high as a football. Another factor that affects the size of the kidney is gender. The kidneys of females are smaller than males and the left kidney is larger than the right kidney, regardless of gender. A decrease in the size of the kidney can be caused by decrease level of blood supply. Aside from gender, age, and race, the kidney size can also be affected by the presence of some diseases. Example of these diseases are; renal dysplasia, renal agenesis, lupus nephritis, and renal paranchymal diseases. In addition

to these, acquired diseases like diabetic nephropathy, glomerulonephritise, interstitial nephritis, renal cell carcinoma and Willims tumors also have effects on the dimensions of the kidney. (WilliamJ,2005).

(1.1.1.5) Normal renal volume:

Renal length and volume are important indicator of the presence or progression of disease. They are also important clinical parameters in the evaluation and follow up of kidney transplant recipients, patients with hypertension and renal insufficiency related to renal artery stenosis, patient with recurrent urinary infection and younger patient with vesicoureteric reflux. Because therapeutic decisions frequently are based on the result of these dimensions, accurate and reproducible methods for assessing renal length and volume are of increasing importance. In additions, an understanding of reference values of normal renal metrics is critical to assess alteration from these values. (Nicholson,2000)

A number of imaging methods are used for calculating the renal volume. Tomographic imaging method, such as x-ray computed tomography (CT) and magnetic resonance imaging (MRI) can acquire three dimensional data to estimate the volume of kidney. In the case of (CT) the need of ionizing radiation and potentially nephrotoxic contrast media limits its place as a routine non invasive imaging method for

measuring kidney volumes. Conversely, MRI has the benefits of acquiring true tomographic data a long any orientation, without the constraints of ionizing radiation and nophrotoxic contrast burden. Although MRI has those previous benefits it is expensive and not available. Ultrasound is not invasive, simple and reliable method used to measure the volume of kidney in two dimensional. (Mariom,2002)

(1.1.2) Renal physiology:

(1.1.2.1) Glomerular filtration:

The glomerular capillaries have large pores in their walls, and the layers of Bowman’s capsule in contact with the glomerulus have filtrations slits. Water together with dissolved solutes (except proteins), can thus pass from the blood plasma to the inside of the capsule and the nephrone tubules. The volume of this filtrate produced by both kidneys per minute is called the glomerular filtration rate (GFR). The (GFR) averages 115mil per minute in women and 125 mil per minute in men. This is equivalent to 180 liter per day (about 45 gallons). Most of the filtrate water must obviously be returned immediately to the vascular system (Born,2005) .

(1.1.2.2) Regulation of GFR:

Vasoconstriction or dilation of afferent arterioles affects the rate of blood flow to the glomerulus, and thus affects the GFR. Changes in

the diameter of afferent arteriole result from both extrinsic regulatory mechanism produced by sympathetic nervous innervation and intrinsic regulatory mechanism produced by the kidneys. The later is called renal auto regulations mechanism (ElaineN,2003) .

(1.1.2.3) Renal auto regulations:

Is the ability of the kidney to maintain a relatively constant (GFR) in the face of fluctuating blood pressures. This is achieved through the effect of locally produced chemicals on the afferent arterioles. When systemic arterial pressure falls towards a mean of 70mm/11g, the afferent arterioles dilate, and when the pressure rises, the efferent arterioles constrict. Blood flow to the glomeruli and GFR can thus remain relatively constant within the auto regulatory range of blood pressure values (Stauart,2006) .

(1.1.2.4) Juxtaglomerular apparatus:

The juxtaglomerular apparatus is the region in each nephron when the afferent arteriole comes into contact with the last portion of the thick ascending limb of the loop. Under the microscope, the afferent arteriole and tube in this small region have a different

appearance than in the other region. The cells in this region secrete the enzyme rennin into the blood. This enzyme catalyzes the conventions of angiotensinogen (a protein) into angiotensin I. Angiotensin I will be converted to angiotensin II by angiotensin converting enzyme (ACE). This convention occurs as the blood passes through the capillaries of the lung (Snell,2004) .

(1.1.2.5) Regulation of blood pressure by the kidneys:

The regulation of the blood by kidneys is done by a system called rennin-angiotensin aldesterone system. When the blood flow is reduced in the renal artery, juxtaglomerular apparatus start to secrete the enzyme rennin into the blood. Condition of salt deprivation, low blood volume, and low pressure in summary cause increased production of angiotensin II in the blood. Angiotensin II exerts numerous effects that produce a rise in blood pressure. This rise in pressure is partly due to vasoconstriction and partly to increase in blood volume. Vasoconstriction of arterioles and small muscular arteries is produced directly by the effect of angiotensin II on the small muscles of these vessels. The increased blood volume is an indirect effect of angiotensin II. Angiontensin II promotes a rise in blood volume by means of two ways or mechanism. The thirst centres in the hypothalamus are stimulated by angiotensin II, and thus more water is ingested, and secretion of aldesterone from the adrenal cortex, is stimulated by angiotensinII, and higher aldesterone secretions causes

more salt and water to be retained by the kidneys, so blood volume will be increased (Figure 1.4) .

The rennin angiotensin-aldesterone system can also work in the opposite direction: high salt intake, leading to high blood volume and pressure normally inhibits rennin secretion, with less angiotensin II formation and less aldesterone secretion, less salt is retained by the kidney and more is excreted in the urine. Unfortunately, many people with chronically high blood pressure may have normal or even elevated levels of rennin secretion (WilliamJ,2005).

(Figure 1-4): Renal-Angiotensin-Aldesterone system(William,2005)

(1.1.3) Renal pathophysiology

(1.1.3.1) Vascular injury to the kidney:

Adequate delivery of blood to the glomerular capillary network is crucial for glomerular filtration and overall salt and water balance. Thus, in addition to the threat of the viability of renal tissue, vascular injury to the kidney may compromise the maintenance of body fluid volume and composition. Involvement of the renal vessels by atherosclerotic, hypertensive, embolic, inflammatory and hematologic disorders is usually a manifestation of generalized vascular pathology.

(1.1.3.1.1) Thromboembolic diseases of the renal arteries**:**

Thrombosis of the major renal arteries or their branches is an important cause of deterioration of renal function, especially in the elderly. It is often difficult to diagnose and therefore requires a high index of suspicion. Thrombosis may occur as a result of intrinsic pathology in the renal vessels or as a result of emboli originating in distant vessel, most commonly fat emboli, emboli originating in the left heart, or “paradoxical” emboli passing from the right side of the circulation via a patent foramen ovale or arterial septal defect. Renal emboli are bilateral in 15 to 30% of cases (Harrison,s,2001).

The clinical presentation is variable, depending on the time course and the extent of the occlusive event. Acute thrombosis and infection, such as follows embolization, may result in sudden onset of flank pain and tenderness, fever, hematuria, leukocytosis, nausea and vomiting. If infarction occurs, renal enzymes may be elevated, namely aspartate amino transferase (AST), lactic dehydrogenese (LDH) and alkaline phosphotase'. Renal function deteriorates acutely, leading in bilateral thrombosis to acute oliguric renal failure. More gradual occlusion of a single renal artery may go undetected. Hypertension usually follows renal infarction and results from rennin release in the peri-infarction zone. Hypertension is usually transient but may be persistent (C Craig,1994).

(1.1.3.1.2) Atheroembolic disease of the renal artery:

Atheroembolic disease typically results from multiple showers of cholesterol containing micro emboli dislodged from atheromatous plaques in large arteries. Such emboli occlude small (150µm to 200µm diameter) vessels in the kidney and in other organs (retina, brain, pancreas, muscles, skin and extremities). Atheroembolic disease usually occurs in an elderly individual with atherosclerotic disease elsewhere and usually follows aortic surgery or renal or coronary arteriography.

Manifestation includes deterioration of renal function (sudden or gradual), mild protein urea, microscopic haematuria and leukocyturia. Urine volume remains normal or fall to oliguric levels depending on severity. Renal ischemia can induce or exacerbate preexisting hypertension. In elderly patient with mild to moderate cholesterol embolization, the remaining nephrons may subsequently undergo injury, likely a result of hyperfiltrations, which may lead to nephritic-range proteinuria. Renal biopsy reveals focal segmental sclerosis. Renal function deteriorates as lower rate in these individuals than in patients with more substantial embolic burdens, and they would be expected to benefit from angiotensin converting enzyme (ACE) inhibitor therapy aimed at lowering intraglomerular pressure in remnant nephrons, even if their systemic blood pressure is in the normal range (Richard,2006) .

(1.1.3.1.3) Renal vein thrombosis (RVT):

Thrombosis of one or both main renal veins occurs in a variety of settings. The pathogenesis is not always clear; particularly when it occurs in so called hypercoagulable states such as may develop in pregnancy, use of oral contraceptives, subjects with nephritic syndrome, or dehydrated infants. Nephritic syndrome accompanying membranous glomerulopathy and certain carcinomas seems to

predispose to development of (RVT), which occurs in a 10 to. 50% of patients with these disorders. (RVT) may exacerbate preexisting proteinuria but is infrequently the cause of the nephritic syndrome. (Gerhard,1985) .

The clinical manifestation depends on the severity and abruptness of its occurrence. Acute cases occur typically in children and are characterized by sudden loss of renal function, often accompanied by fever, chills, lumbar tenderness (with kidney enlargement), leukocytosis, and hematuria. Hemorrhagic infarction and renal rupture may lead to hypovolemic shock. In young adults (RVT) is usually suspected from an unexpected and relatively acute or subacute deterioration of renal function and/or exacerbation of proteinuria and hematuria in the appropriate clinical setting. In case of gradual thrombosis, usually occur in the elderly, the only manifestation maybe recurrent pulmonary emboli or development of hypertension. The definitive diagnose can only be established through selective renal venography with visualization of the occluding thrombus. Short of angiography, ultrasound and magnetic resonance imaging (MRI) often provides definitive evidence of thrombus (Harison,s,2001).

(1.1.3.1.4) Renal artery steno sis (Renal ischemia):

Renal artery stenosis is narrowing of the renal artery most often cause by atherosclerosis or fibro muscular dysplasia. This narrowing of

the renal artery can impede blood flow to the target kidney. Hypertension and atrophy or the affected kidney may result from renal artery stenosis ultimately leading to renal failure if not treated .

Most cases of renal artery stenosis are asymptomatic, and the main problem is high blood pressure that cannot be controlled with medication. Deterioration in renal function may develop, if both kidneys are poorly supplied, or when treated with ACE (Angiotensin Converting Enzyme) inhibitions is initiated. Some patients present with sudden left ventricular heart failure.

The etiology of renal artery stenosis is atherosclerosis which is predominant cause of renal artery stenosis in the majority of patients, usually those with a sudden onset of hypertension at age of 50 and older. Fibro muscular dysplasia is the predominant cause in young patient, usually female under 40 years of age. A variety of other causes exist. These include arteritis, renal artery aneurism, extrinsic compression (Neoplasm), neurofibromatosis and fibrous bands. (Pickering,1998).

The path physiology of the renal artery stenosis started when the macula densa of the kidney senses a decreased systemic blood pressure owing to the reduced blood flow through the narrowed artery. The response of the kidney to this perceived decreased blood pressure is activation of the rennin-angiogenesis aldesterone system, which normally counteracts low blood pressure but in this case leads to

hypertension. The decreased perfusion pressure (caused by stenosis) leads to decrease blood flow, hypoperfusion to the kidney and a decrease in glomerular filtration rate (GFR). If the stenosis in long standing or severe, the GFR in the affected kidneys never increase again and renal failure is the result.(Kerijnen,1998)

Renal artery stenosis can be diagnosed by angiography or arteriography, computerized tomography, magnetic resonance imaging (MRI) and ultrasonography see figure (1.5). Arteriography is the most invasive procedure, since a catheter or small tube needs to be threaded through the arteries in the groin into the renal artery and contrast injected. This test will show how much narrowing is there and if it is found, stending may be done as a part of treatment. Computerized tomography (CT) will show all the blood vessels in the abdomen as well as the other organs. The intravenous contrast used may have the potential to cause some kidney damage or deterioration of renal function and the procedure-related complications at the site of arterial puncture or catheter induced embolism. (MRI) produce excellent contrast enhanced angiogram without the risk of contrast media and radiation exposure. It provides accurate information about the number of renal arteries, the size of the kidney and the presence of anatomical variations, but on the other hand, MRA is expensive and its availability is limited. Doppler ultrasound is simple non invasive method which can be used to approximate the amount of blood flowing

through the renal artery to the kidney, and to measure the velocity of blood. It has a high sensitivity in expert hands. The benefits and risk of each procedure needs to be assessed for each patient to decide what would be most appropriate in a given situation.

(C Craig,1994).

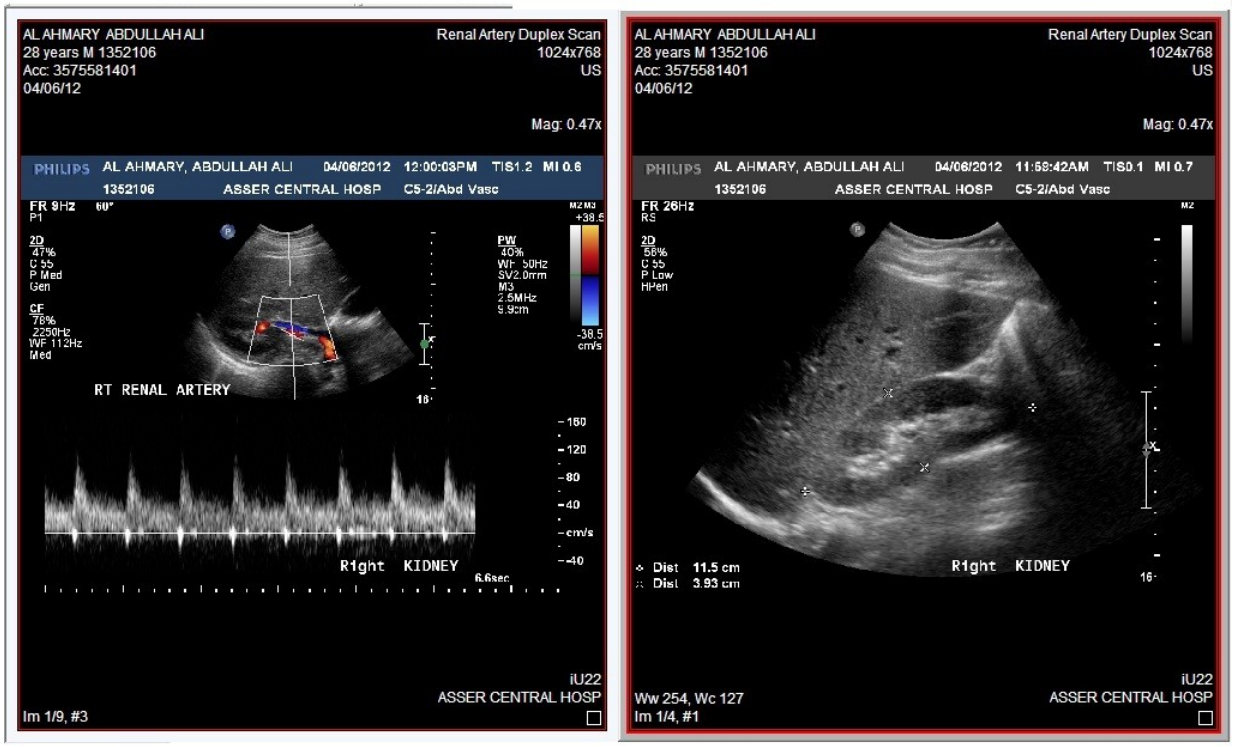


Figure (1.5) : Renal artery stenosis detected by ultrasound (see appendixIV)

(1.1.3.2)Chronic kidney disease (CKD):

Chronic kidney disease (CKD) is a progressive loss in renal function over a period of months or years. The symptoms of worsening kidney function are unspecific, and might include feeling generally unwell and experiencing a reduced appetite. Often, chronic kidney disease is diagnosed as a result of screening of people known to be at risk of the kidney problem, such as those with high blood pressure or diabetes and those with a blood relative with chronic kidney disease. Chronic kidney disease may also be identified when it leads one of its recognized complications, such as cardiovascular disease, anemia and pericarditis**.**

The prevalence of (CKD) over the world is high. In Canada 1.9 to 3.3 million people have chronic kidney disease. UK estimates suggest that 8.8% of the population of Great British and North Ireland have symptomatic (CKD). There are few available data about the prevalence of chronic kidney disease and its risk factors in general population of the kingdom of Saudi Arabia. It is estimated that (CKD) in older people is higher than adults and the overall prevalence of CKD was 5.7% (Alsuwaida,2010).

CKD is initially without specific symptoms and can only be detected as an increase in serum creatinine or protein in the urine. As the kidney function decreases, blood pressure is increased due to fluid overload and production of vasoactive hormones, urea accumulates leading to azotemic and ultimately uremia, potassium accumulates in

the blood; erythropoietin synthesis is decreased, fluid volume overload, hyperphosphatemia and metabolic acidosis. People with (CKD) suffer from accelerated atherosclerosis and are more likely to develop cardiovascular diseases than the general population. Patients afflicted with (CKD) and cardiovascular diseases tend to have significantly worse prognosis than those suffering only from the later.(Kumar,2003).

The most common causes of (CKD) are diabetes mellitus, hypertension and glomerulo- nephritis**.** Together these cause approximately 75% of all adult cases. Certain geographic areas have a high incidence of human immunodeficiency virus (HIV) nephropathy. Historically kidney disease has been classified according to the part of the renal anatomy that is involved as: firstly “vascular, which include bilateral renal artery stenosis, ischemic nephropathy, hemolytic-uremic syndrome and vasculitis. Secondly glomerular, comprising a diverse group and sub classified into primary glomerular disease and secondary glomerular disease. Thirdly tubulo interstitial disease, including polycystic kidney disease, drug and toxin- induced chronic tubulointerstitial nephritis and reflux nephropathy. Lastly obstructive such as bilateral kidney stones and diseases of prostate. In many (CKD) patients, previous renal disease or other underlying diseases are already known. A small number of patients’ presents with (CKD) have unknown cause.(Underwood,2004).

It is important to differentiate between (CKD) and acute renal failure, because acute renal failure (ARF) can be reversible. Abdominal ultrasound is commonly performed, in which the size of the kidney are measured. Kidney with (CKD) are usually smaller (<9cm) than the normal kidney with notable exceptions such as in diabetic nephropathy and polycystic kidney disease. Another diagnostic method that helps to differentiate (CKD) and (ARF) is a gradual rise in serum creatinine over several months or years as opposed to a sudden increase in the serum creatinine (several days or weeks). Additional test may include nuclear medicine (MAG3) scan to confirm blood flows and establish the differential function between the two kidneys. (C Craig,1994).

All individuals with (GFR) <60ml/min/1.73m/for 3 months are classified as having (CKD), irrespective of the presence or absence of renal damage. The rationale for including these individuals is that the reduction in the kidney function to this level or lower represents loss of half or more of the adult level of normal kidney function, which may associated with a number of complications. All individuals with kidney damage are classified as having (CKD) irrespective of the level of (GFR). The loss of protein in the urine is regarded as independent marker for worsening of renal function and cardiovascular disease. (CKD) can be classified into:

Stage 1: Slightly diminished function, kidney damage with normal or high GFR **(>90).**

Stage 2: Mild reduction in (GFR) (60-89) with kidney damage.

Stage 3: Moderate reduction in (GFR) (30-59).

Stage 4: Severe reduction in (GFR) (15-29).

Stage 5: Established kidney failure (GFR) (<15). (Robin,2005).

(1.2) Pathology of Hypertension

(1.2.1): Definition of hypertension

Hypertension is the term used to describe high blood pressure. Blood pressure is a measurement of the force against the walls of the arteries as the heart pumps blood through the body. Blood pressure reading are measured in millimeters of mercury (mm/Hg) and usually given as two numbers, for example 120 over 80 (written 120/80 mm/Hg). One or both of these numbers can be too high. The top number is the systolic pressure, which is defined as blood pressure in vessels during the heart beat. It is considered high if it is over 140 most of the time and it considered normal if it is below 120 most of the

time. The bottom number is the diastolic pressure, which is defined as blood pressure in vessels between heart beat. It s considered high, if it is over 90 most of the time and it is considered normal if it is below 80 must of the time. Pre-hypertension can be considered when the systolic blood pressure is between 120 and 139 most of the time or the diastolic blood pressure is between 80 and 89 most of the time. This is according to the fifth report of Joint National Committee on detection, evaluation and treatment of high blood pressure in world health organization (WHO) (Singh,2000).

The prevalence of arterial hypertension is increasing globally. In develop countries like United Kingdom and the United states of America, 37% and 25% of their adults had hypertension respectively, while the reported prevalence was 28.5% in Kuwait and 26.3% in Egypt (Kearney,2004). Studies have revealed that the prevalence of hypertension is increasing in Saudi Arabia . The highest prevalence of hypertension in Saudi Arabia has been reported from AL-Qasim region (30%), while the prevalence in the age group of 30-70 years in both sex was 26.1% (Al Nozha,1998) . In the Aseer region a survey was conducted in Semi-urban and rural areas in South Western of Saudi Arabia to study the prevalence of hypertension among the people living in these areas. There were 442 cases (12%) of hypertension among 3969 respondent subjects. The report concluded that further

studies are needed to clarify whether the disease is altitude dependant or not.(Mahfouz,1993)

Both environmental and genetic factors may contribute to regional and racial variations of blood pressure and hypertension prevalence. Studies of societies undergoing “acculturation” and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension. It has been estimated that 60% of hypertension are > 20% overweight. Among population, hypertension prevalence is related to dietary (Nacl) intake, and the age related increase of blood pressure may be augmented by a high (Nacl) intake. Low dietary intake of calcium and potassium may also contribute to the risk of hypertension. Additional environmental factor that may contribute to hypertension include alcohol consumption, physical stress and low level of physical activities (Elaine,2003).

Lastly can we add living in high altitude area will be another environmental factor that may cause hypertension? This study is established to show whether there is a relation between hypertension and high altitude.

(1.2.2) Classification of hypertension:

Blood pressure is usually classified based on the systolic and diastolic pressure. A systolic or diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as pre-hypertension or hypertension. Hypertension has several sub-classification including, hypertension stage I, hypertension stage II and isolated hypertension. Isolated hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly. These classifications are made after averaging a patient's resting blood pressure reading taken on two or more office visits. Individual older than 50 years are classified as having hypertension if their blood pressure is consistently at least 140 mm/Hg systole or 90 mm/Hg diastolic. Patients with blood pressure higher than 130/80 mm/Hg with concomitant presence of diabetes mellitus or kidney disease require further treatment. Hypertension is also classified as resistant, if medications do not reduced blood pressure to normal levels. Exercise hypertension is an excessively high elevation of blood pressure during exercise. The range considered normal for systolic values during exercise is between 200 and 230 mm/Hg. Exercise hypertension may indicate that an individual is at risk for developing hypertension at rest. Hypertension is also classified as either primary (essential) or secondary. About 90% of cases are termed

primary hypertension which refers to high blood pressure for which no medical causes can be found. The remaining 10% of cases (secondary hypertension) are caused by other conditions that affect the kidney, heart, arteries or endocrine system. (Davidson,s,2010) (table 1.1)

BP Classification	**Systole mm/Hg**	**Diastole Mm/Hg**
Normal	< 120	And < 80
Pre-hypertension	120-139	Or 80-89
Stage I hypertension	140-159	Or 90-99
Stage II hypertension	≥ 160	Or ≥ 100
Isolated hypertension	≥ 140	And < 90

Table (1-1): Classification of hypertension(Elaine,2003)

(1.2.3) Mechanism of hypertension:

To provide a framework for understanding the pathogenesis and treatment options of hypertension disorders, it is useful to understand factors involved in the regulation of both normal and elevated arterial pressure. Cardiac output and peripheral resistance are the two determinant of arterial pressure (Figure1.6). Cardiac out put is determined by stroke volume and heart rate, stroke volume is related to myocardial contractility and the size of the vascular compartment.

Peripheral resistance is determined by functional and anatomical changers in small arteries (Kumar,2003) .

Stroke volume

Cardiac out put

Arterial pressure **Vascular structure**

Peripheral resistance

Vascular function

(Figure1.6) ; Determinant of arterial pressure (Kumar,2003)

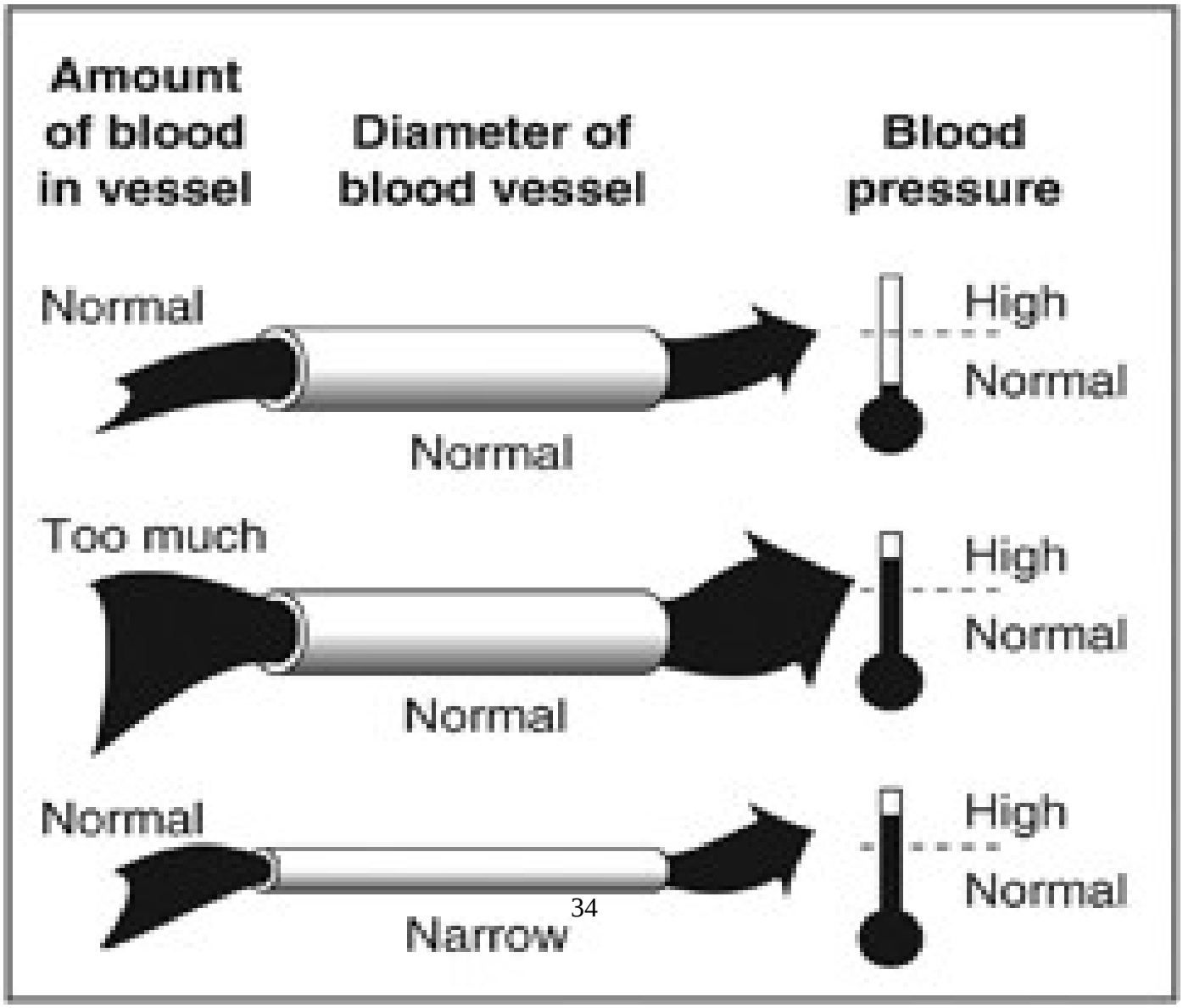
(1.2.4) Patho physiology of renal hypertension:

Most of the mechanism associated with secondary hypertension is generally fully understood. However, those associated with essential hypertension are far less understood. What is known is that cardiac out put is raised early if the disease course, with Total Peripheral Resistance (TPR) normal, over time cardiac out put drops to normal level but (TPR) is increased. Three theories have been proposed to explain this:

1. Inability of the kidney to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance.
2. An over active renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume leads to hypertension.
3. An over active sympathetic nervous system, leading to increase stress responses.

It is also known that hypertension is highly heritable and polygenic and a few candidate genes have been postulated in the etiology of this condition. Recently work related to the association between essential hypertension and sustained endothelial damage has gained popularity among hypertension scientists. It remains unclear however whether endothelial changes precede the development of hypertension or whether such changes are mainly due to long standing elevated blood pressure (Figure1.7).

(Gerhard,1985)



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Figure(1.7): pathophysiology of hypertension (Harrison,s,2001)

(1.2.5) Causes of hypertension:

Most of the time, if no cause is identified for hypertension, this is called essential hypertension. Essential hypertension is the most prevalent type of hypertension, affecting (90-95%) of hypertensive patients. Although no direct cause has identified, there are many factor such as sedentary lifestyle, smoking, stress, potassium deficiency

(hypo kalemia), obesity (body mass index greater than 25), sodium sensitivity, alcohol intake and vitamin D deficiency that increase the risk of developing hypertension. Risk also increases with aging, some inherited genetic mutations and having a family history of hypertension. An elevation of rennin and sympathetic nervous system over activity are other risk factors for hypertension. Insulin resistance which is component of syndrome or the metabolic syndrome is also thought to contribute to hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

(Davidson,s,2010)

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it treated differently to essential hypertension, by treating the underlying cause of the elevated blood pressure. Many conditions cause hypertension some are common and well recognize secondary causes such as Cushing's syndrome, which is a condition where the adrenal glands over produce the hormone cortisol. In addition, hypertension is caused by other conditions that cause hormone changes such as hyperthyroidism, hypothyroidism and certain tumors of adrenal medulla. Other common causes of secondary hypertension include kidney disease, pre-eclampsia during pregnancy, coarctation of the aorta and certain drugs.(Harison,s ,2000) .

(1.2.6) Signs and symptoms:

Mild to moderate essential hypertension is usually a symptomatic. Accelerated hypertension is associated with headache, drowsiness, confusion, vision disorder, nausea and vomiting symptoms which are collectively referred to as hypertensive encephalopathy. Hypertensive encephalopathy is caused by severe small blood vessel congestion and brain swelling, which is reversible if blood pressure is lowered. Some signs and symptoms are especially important in newborns and infants such as failure of thrive, seizures irritability, lack of energy and difficulty in breathing. In children, hypertension can cause headache, fatigue, blurred vision, nosebleeds and facial paralysis.(Richard,2006)

Some additional sign and symptoms suggest that the hypertension is caused by disorders in hormone regulation. Hypertension combined with obesity distributed on the trunk of the body, accumulated fat on the back of the neck, wide purple mark on the abdomen or the recent on set of diabetes suggests that an individual has a hormone disorders known as Cushing’s syndrome. Hypertension caused by other hormone disorders such as hyperthyroidism, hypothyroidism or growth hormone excess will be accompanied by additional symptoms specific to these disorders. Hypertension in pregnant woman is known as pre-eclampsia. Pre-eclampsia can progress to a life threatening condition called

eclampsia, which is the development of protein in the urine, generalized swelling and severe seizures. Other symptoms indicating that brain function is becoming impaired may precede these seizures such as nausea, vomiting, headache and vision loss.(Richard,2006) .

(1.2.7) **Diagnose of hypertension:**

Hypertension is generally diagnosed on the basis of persistently high blood pressure. Usually this requires three separate sphygmomanometer measurement at least one week a part. Initial assessment of hypertensive patient should include a complete history and physical examination. Exceptionally, if the elevation is extreme or symptoms of organ damage are present, the diagnose may be given and treatment started immediately. Once the diagnose of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in pre adolescent children, with most cases caused by renal diseases. Primary or essential hypertension is more common in adolescents and has multiple risk factors including obesity, and family history of hypertension. Laboratory test can also be performed to identify possible caused of secondary hypertension and determine if hypertension has caused damage to the heart, eyes and kidneys.

Test of urine sample for protein is used as secondary indictor of kidney disease. Glucose testing is made to determine if diabetes mellitus is present. Electro cardiogram (ECG) testing is done to check for evidence of the heart being under strain from high blood pressure. A chest x-ray may be performed to look for signs of the heart enlargement or damage of heart tissues. Ultrasound examination is made to determine if there is damage in kidney tissues.

(Underwood,1998) .

(1.2.8) **Complications of hypertension:**

Hypertension is the most important risk factor for death in industrialized countries. It increases hardening of the arteries thus predisposes individuals to heart disease, peripheral vascular disease and stroke. The complications include:

(1.2.8.1) Blood vessels:

In larger arteries (> 1mm in diameter) the internal elastic lamina is thickened, smooth muscle is hypertrophied and fibrous tissue is deposited. The vessels dilate and become tortuous, and their walls become less compliant. In small arteries less than 1mm) hyaline arteriosclerosis occurs in the wall, the lumen narrows and aneurysms may develop. Widespread atheroma develops and may

lead to coronary and cerbrovascular disease, particularly if other risk factors (example: smoking, hyperlipidaemia, diabetes) are present.

These structural changes in the vasculature often perpetuate and aggravate hypertension by increasing peripheral vascular resistance and reducing renal blood flow, there by activating the renin-angiotensin aldesterone system. Hypertension is a major risk factor in the pathogenesis of aortic aneurysm and aortic dissection. (Kumar,2003)

(1.2.8.2) Central nervous system:

Stroke is a common complication of hypertension and may be due to cerebral hemorrhage or infarction. Carotid atheroma and transient ischemic attacks are more common in hypertensive patients. Subarachnoid hemorrhage is also associated with hypertension. Hypertensive encephalopathy is a rare condition characterized by high blood pressure and neurological symptoms including transient disturbances of speech or vision, paraesthesiae, disorientation, fits and loss of consciousness. Papilla edema is common. Computerize tomography (CT) of the brain often shows hemorrhage in and around the basal ganglia; however the neurological deficit is usually reversible if the hypertension is properly controlled.(Harison,s,2001)

(1.2.8.3) Retina:

The optic fundi reveal a gradation of changes linked to the severity of hypertension, fundoscopy can therefore provide an indication of the arteriolar damage occurring else where. “Cotton wool” exudates are associated with retinal ischemia or infarction, and fade in a few weeks. “Hard” exudates (small, white, dense deposits of lipid) and micro aneurysms are more characteristic of diabetic retinopathy. Hypertension is also associated with central retinal vein thrombosis.(Davidson,s,2010)

(1.2.8.4) Heart:

The excess cardiac mortality and morbidity associated with hypertension are largely but to a higher incidence of coronary artery disease. High blood pressure places a pressure load on the heart and may lead to left ventricular hypertrophy with a forceful apex beat and fourth heart sound. ECG or echocardiography evidence of left ventricular hypertrophy is highly predictive of cardio vascular complications and therefore particularly useful in risk assessment. A trial fibrillation is common and may be due to diastolic dysfunction caused by left ventricular hypertrophy or the effect of coronary artery disease. Severe hypertension can cause left ventricular failure in the absence of coronary artery disease, particularly when renal function, and therefore sodium excretion is impaired. (Davidson,s,2010)

(1.2.8.5) Kidneys:

Long standing hypertension may cause proteinuria and progressive renal failure by damaging the renal vasculature. There are two aspects to describe the relationship of the kidney and high blood pressure: many renal disease lead to hypertension and hypertension leads to renal damage.

(1.2.8.6) Malignant (accelerated phase) hypertension:

This rare condition may complicate of any etiology and is characterized by accelerated micro vascular damage with necrosis in the walls of small arteries and arterioles and by intravascular thrombosis. The diagnosis is based on evidence of high blood pressure and rapidly progressive end organ damage such as retinopathy, renal dysfunction especially proteinuria and/or hypertensive encephalopathy. Left ventricular failure may occur and, if this is untreated death occurs within months (Kumar,2003).

(1.2.9) **Secondary hypertension (Non-essential):**

As noted earlier, in only small minority of patients with elevated arterial pressure can specific cause be identified. Yet these patients should not be ignored for at least two reasons: correction of the cause may cure their hypertension and these secondary forms of the disease may provide insight into the etiology of essential hypertension. Nearly all the secondary forms of hypertension are

related to an alteration in hormone secretion and/ or renal function. One example of secondary hypertension is renal hypertension

(1.2.9.1) Renal hypertension:

Renal hypertension is hypertension produced by renal disease as a result of either a dearrangement in the renal handling of sodium and fluids leading to volume expansion, or an alteration in renal secretion of vasoactive materials resulting in a systemic or local damage in arterial tone. The main subdivisions of renal hypertension are renovascular hypertension, including pre-eclampsia and eclampsia, and renal parenchyma hypertension. A simple explanation of renal vascular hypertension is that decreased perfusion of renal tissue due to stenosis of a main branch renal artery, activates the renin-angiotensin system. Circulating angiotensin II elevates arterial pressure by directly causing vasoconstriction, by stimulating aldeslerone secretion with resulting sodium retention and/ or by stimulating the adrenergic nervous system. In practice, only about one half of patients with renovascular hypertension have an absolute elevation in rennin activity in plasma, although when rennin measurement are referenced against an index of sodium balance, much higher reaction have in appropriately high values .The clinical finding in renovascular hypertension include the following:

a- Hypertension that is difficult to control with medical treatment.

b- Hypertension associated with renal failure or renal insufficiency.

c- Severe hypertension (diastolic pressure greater than 120mm/Hg)

d- Onset of hypertension before age 30 or after age 50.

e- Abrupt onset of hypertension.

f- Generalized atherosclerosis.

g- Negative family history of hypertension.

h- Abdominal bruit.

Activation of renin-angiotensin system has also been offered as an explanation for the hypertension in both acute and chronic renal parenchyma disease. In this formulation, the only different between renovascular and renal parenchyma hypertension is that the decreased perfusion of renal tissue in the later case results from inflammatory and fibrotic changes involving multiple small intra renal vessels. There is enough difference between the two conditions, however, to suggest that other mechanisms are active in renal parenchyma disease specifically. These differences are;

1. Peripheral plasma rennin activity is elevated for less frequently in renal parenchyma than in renovascular hypertension.
2. Cardiac out put is said to be normal in renal parenchyma hypertension, but slightly elevated in renovascular hypertensions.
3. Circulatory responses to tilting and to the valsalva maneuver are exaggerated in the later condition.
4. Blood volume tends to be high in patient with severe renal parenchyma diseases and low in patients with severe renovascular hypertension.

Alternative explanations for the hypertension in renal parenchyma disease include the possibilities that the damage kidneys:

1. Produce an unidentified vasopressor substance other than rennin.
2. Fail to produce a necessary humoral vasodilator substance.
3. Fail to in activate circulatory vasopressor substance.
4. In effective in disposing of sodium.

In the last point the retaining sodium would be responsible for the hypertension as outlined. Although all these explanations, including participation of the rennin angiotensin system, probably have some validity in individual patients, the hypothesis involving sodium retention is particularly attractive. It is supported by the observation

that those patients with chronic pylonephritis or polycystic renal disease who are salt wasters not develop hypertension and by the observation that removal of the salt and water by dialysis or diuretics is effective in controlling arterial pressure in most patients, with renal parenchyma disease.

A rare form of renal hypertension results from the excess secretion of rennin by juxtaglomerular cell tumor or nephroblastomas. The initial presentation is similar to that of hyperaldosteronism, with hypertension, hypokalemia and overproduction of aldosterone. However, in contrast to primary aldosteronism, peripheral rennin activity is elevated instead of subnormal. This disease can be distinguished from other forms of secondary aldosteronism by the presence of normal renal function and unilateral increase in renal rennin concentration without a renal artery lesion. (C.Craig,1994)

(1.3) **High altitude physiology and path physiology:**

(1.3.1): Definition

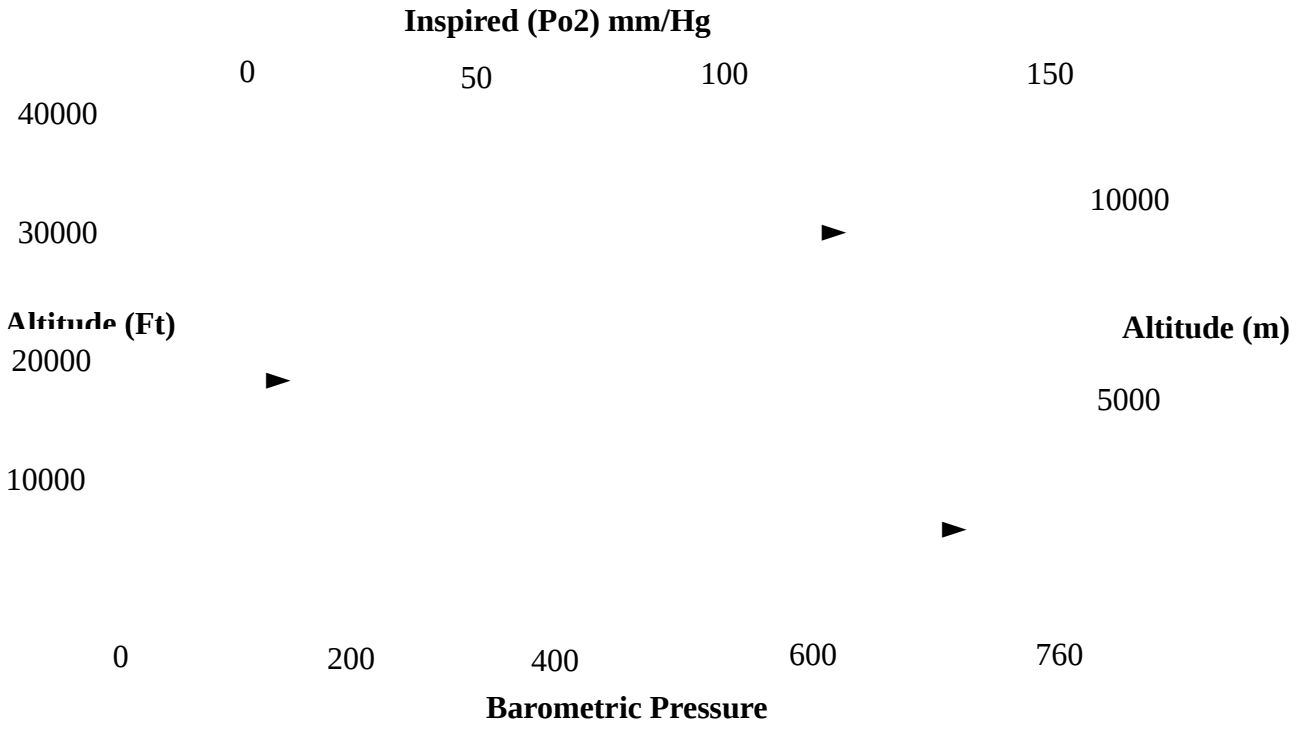
The troposphere is the lowest portion of the atmosphere and envelopes the earth's entire surface. Within the troposphere, barometric pressure falls as altitude increases. The concentration of oxygen in air remains constant so, as the barometric pressure decreases, the partial pressure of oxygen decreases proportionately. This condition is referred to as hypobaric hypoxia (Table1.2) (Figure1.8) (Bertges,1987)

High altitude physiology maybe divided into the study of short term changes that occur with exposure to hypobaric hypoxia and studies of longer term acclimatization and adaptation. Acute exposure to the ambient atmosphere at extreme altitude (above 8,000m) is fatal. Acclimatization is the set of beneficial processes where by lowland humans respond to a reduced inspired partial pressure of oxygen. This changes tend to reduce the gradient of oxygen partial pressure from ambient to air tissues and are distinct from the pathological changes that lead to altitude illness. Adaptation to high altitude describes changes that have occurred over a number of generations as a result of natural selection in a hypobaric hypoxic environment, and this can be observed in some group of high altitude residents . In spite of hypoxia associated with high altitude, many people live at elevation over 3,000m. A degree of acclimatization occur when human ascent to these altitudes. One of the most useful responses to high altitude is hyperventilation. The cause of

hyperventilation is hypoxic stimulation of peripheral chemoreceptors. The resulting low partial pressure of carbon dioxide (PCo2) and alkalosis tend to work against this increase in ventilation, but after a day or so, the cerebrospinal fluid (CSF) PH is brought partly back by movement of bicarbonate out of the (CSF) and after 2 or 3 days the (PH) of the arterial blood is returned to near normal by renal excretion of bicarbonate. High altitude illness maybe divided into the acute syndromes that affect lowland or highland residents ascending to altitudes greater than those to which they are accustomed, and the chronic conditions that affect individuals resident at high altitude for long period. The acute adult syndromes of high altitude are acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE) (Johan,1995) .

Altitude (m)	**Atmospheric Pressure mm/Hg**	**(Po2) in air mm / Hg**	**(Po2) in arterial Blood mm/Hg**
Sea level	760	159	100
2,000	707	148	92
4,000	656	137	85
6,000	609	127	79
8,000	564	118	74
10,000	523	109	69
20,000	349	73	35
30,000	226	47	19

Table (1-2): Effect of Altitude on partial oxygen pressure (PO_2) (John,1995)



(Figure 1.8): Relationship between altitude and barometric pressure (West,1977)

(1.3.2) **Hypoxia**

Hypoxia is a pathological condition in which the body as a whole (generalized hypoxia) or a region of the body (tissue hypoxia) is deprived of adequate oxygen supply. Variation in arterial oxygen concentration can be part of the normal physiology, for example during strenuous physical exercise. Mismatch between oxygen supply and its demands to the cellular level may result in hypoxic condition. Hypoxia in which there is complete deprivation of oxygen supply is referred to anoxia. Hypoxia differs from hypoxemia. In the later, the oxygen concentration within the arterial blood is abnormally low. It is possible to experience hypoxia and have low oxygen content (Example: due to anemia) but maintain high oxygen partial pressure (Po_2). Generalized hypoxia occurs in healthy people when they ascent to high altitude, where it causes altitude sickness leading to potentially fatal complications; high altitude pulmonary edema and high altitude cerebral edema. (West,1977)

(1.3.2.1) **Classification of hypoxia:**

Hypoxia can be divided into three types:

(1.3.2.1.1) Hypoxemic hypoxia:

Is generalized, an inadequate supply of oxygen to the body as a whole. The term specifies hypoxia caused by low partial pressure of oxygen in arterial blood. In the other causes of hypoxia, partial pressure of oxygen in arterial blood is normal.

Hypoxemic hypoxia maybe due to; low partial pressure of atmospheric oxygen such as found at high altitude or due to low partial pressure of oxygen in the lungs when switching from inhaled anesthesia to atmospheric air. It can be also due to decrease in oxygen saturation of the blood caused by sleep apnea. Inadequate pulmonary ventilation and shunt in the pulmonary circulation can also leads to hypoxemic hypoxia .

(1.3.2.1.2) Histotoxic hypoxia:

In this type of hypoxia quantity of oxygen reaching the cell is normal, but the cells are unable to effectively use the oxygen due to disabled oxidative phosphorylation enzymes.

(1.3.2.1.3) Ischemic or stagnant hypoxia:

In this type there is a local restriction in the flow of well-oxygenated blood. So the oxygen supplied to the region of the body is then insufficient for its need. Examples are cerebral ischemia, ischemic heart disease and intra uterine hypoxia (Cymerman,2009)

(1.3.2.2) **Mechanism of Hypoxia:**

After mixing with water vapour and expired (Co2) in the lung, oxygen diffuses down a pressure gradient to enter arterial blood where its partial pressure is about 100mm/Hg. Arterial blood flow delivers oxygen to the peripheral tissues, where it again diffuses down a pressure gradient into the cells and into their mitochondria. These cytoplasmic structures strip hydrogen from fuels (glucose, fats and

amino acid) to burn with oxygen to form water. The fuel carbon is oxidized to form (Co2), which diffuses down its partial pressure gradient out of the cells into venus blood to finally be exhaled by the lungs. If oxygen delivery to the cells is insufficient for the demands (hypoxia), hydrogen will be shifted to pyruvic acid converting it to lactic acid. This temporary measure (anaerobic metabolism) allows small amounts of energy to be produced. Lactic acid builds up in tissues and blood is a sign of inadequate mitochondrial oxygenation, which may be due to hypoxemia, poor blood flow or combination of both (West,2004)

(1.3.3) **General characteristic of high altitude illness:**

High altitude illness is a spectrum of diseases related to hypobaric hypoxia and its consequences. It includes acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE). The diagnose of these diseases depends on the history and physical examinations.

(1.3.3.1) Acute Mountain Sickness (AMS):

The first description of (AMS), written in 32 to 37 b.c. is attributed to Tokan, a Chinese governmental official who noted “A man’s face turns pale, his head ached and he begins to vomit” when crossing the Himalayan Kilak pass. The occurrence of AMS depends primary on the rate of ascent, the altitude attained and

individual person’s susceptibility. AMS affects 15 to 30 percent of Colorado resort sikiers**,** 50 percent of climbers on mountain Mekinley,70 percent of climbers on mountain Rainier and 25 to 50 percent of climbers who trek to the base of Mount Everest. (West,2004)

Symptoms include, headache, fatigue, weakness, gastro intestinal upset, difficulty sleeping and light theadedness’. According to the 1991 international hypoxia symposium at the Lake Louise, Canada, AMS can de diagnosed when headache and one other symptom are present in the setting of a recent gain in altitude. The headache is probably caused by a mild increased in intracranial pressure and is typically throbbing, bitemporal or occipital, worse at night or in the early morning, and worse in valsalvamaeuver or when bending forward. Dyspnea on exertion is common at altitude, but dyspnea at rest indicates more severe (AMS). Cough at ataxia may occur in severe (AMS). Similar symptoms may occur as a result of viral illness, hangover, exhaustion or dehydration. (Zafren 1997 and Porcell,1995).

(1.3.3.2) High Altitude Pulmonary Edema (HAPE):

Travelers to altitude over (2,500m) will develop (HAPE) depending on age, sex and the rate of ascent. (HAPE) is a form of non carcinogenic pulmonary edema and is associated with marked pulmonary hypertension. It is more common in patients under 20

years of age. The Lake Louise symposium proposed diagnostic criteria for (HAPE). In the setting of the recent gain in altitude, at least two of the following symptoms must be present: dyspnea at rest, cough, weakness or decrease exercise performance chest tightness or congestion. In addition, at least two of the following signs must be present; rales or wheezing in at least one lung field, central cyanosis, tachycardia or tachypnea. (HAPE) usually occurs at night one to three days after an ascent is begun. It is a medical emergency and the most common cause of death from high altitude.(Hultgren,1996)

(1.3.3.3) High Altitude Cerebral Edema (HACE):

(HACE) constitutes the progression of severe AMS or HAPE to include involvement of the brain, causing encephalopathy. It is probably related to vasogenic cerebra edema, usually in increased intracranial pressure. Patients often have severe lassitude and altered consciousness, but the most sensitive indication for HACE my be ataxia (Mardoch,1995)

(1.3.3.4) Other altitude related diseases:

High altitude retinopathy is related to hypoxia and is manifestation by cotton-wool exudates, tortuosity and dilation of retinal vein and scotomata. It is commonly occurring at altitude over 5,000m (16,000ft). It is usually a symptomatic and usually resolve after

one to two weeks even if the patient remains at altitude. Peripheral edema may develop in the hand, face and ankle, and can be treated with diuretics in the absence of (AMS). (Bezruchka,1992)

Thrombotic events such as pulmonary embolus, stroke and Venus thrombosis are a greater danger at high altitudes than at sea level, probably because of the combination of dehydration, Polycythemia, cold and constrictive clothing. Bad whether can force prolonged period of inactivity, causing venus stasis, which may also contribute to thrombosis. To avoid venus stasis and thrombotic event, patient should advised to keep active and well hydrated, and to descend immediately if serious complications arise.(Anerback,1995)

High altitude, active immunity and B cell function remain normal, white T cell function impaired. This effect is probably related to the release of adrenocorticotrophin hormone (ACTH), cortisol and endorphins, and result in increased susceptibility to bacteria (not viral) infection. People at altitude, especially those with (AMS), show an increased incidence of infectious symptoms such as coryz**,** cough, sore throat, and diarrhea. (mardoch,1995)

High altitude pharyngitise and bronchitis are almost universal in people who spend over two weeks at altitude higher than approximately 5,500m (18,000ft). Pharyngitise and bronchitis are probably caused by the effect of cold dry air on the respiratory mucosa, especially with hyperventilation. Mouth breathing vasomotor

rhinitis is common and can be treated with a decongestant nasal spray. Bronchitis can cause cough fits, which can be disabling. Patients should be advised to wear a facemask, such on hand candy and drink plenty of fluids to decrease the problems .

Ultraviolet Keratitise (Snow blindness) occurs when bright sun reflecting off snow causes corneal burns. Damage can occur in one hour, but symptoms may not develop for six to 12 hours. Patients have severe pain in the eyes, photophobia, tearing, chemosis, conjuctival erythema, and eyelid swelling. The keratitis usually resolves spontaneously in 24 hours, snow blindness can be prevented by wearing sunglasses.

(Zafren K,1997)

(1.3.4) **Normal kidney physiology at high altitude:**

Changes in renal function at high altitude arise from the direct effect of hypoxia on the kidneys, as well as from the multiple compensatory adaptations. This includes changes in ventilation, cardiac out put, sympathetic nervous activity and erythropoiesis**.** Dieresis and natriuresis with accompanying potassium and bicarbonate excretion occur with acute reduction in inspired oxygen. In high altitude residents, renal blood flow is decreased 12% and renal plasma flow is also decreased by 30 to 40% as a result of secondary polycythemia. Long term residence reduces also the Glomenular filtration rate but tubular function is maintained because a lower GFR

reduces reabsorptive work and oxygen consumption. Sodium excretion in response to Angiotensin infusion and the capacity to excrete water and salt loads and maximally concentrate urine with water deprivation or vasopressin are also preserved in chronic hypoxia. (Ramirez,1998)

Over several days from hypoxia, the kidneys increase bicarbonate excretion to compensate for respiratory alkalosis. Hypoxia also may increase urinary protein excretion. Protein-urea is greater in patient at high altitude who smoke and have hyperlipidemia . In response to low arterial pressure, interstitial cells increase erythropoietin production and this will rise hemoglobin and red blood cells count . Other factors that may exacerbate renal hypoxia include anemia and hypertension. Severe normovolemic hemodilution in healthy rates reduced cortical micro vascular (Po2) from 70 to 37 mm/Hg and medulla (Po2) from 53 to 28mm/Hg. Hypertension may also create further hypoxia stress as suggested by data in normoxic hypertensive rats, in which renal cortical (Po2) was 100mm/Hg (Johannes,2007)

(1.3.5) **Effect of high altitude on chronic kidney disease (CKD);**

Few studies have addressed the effects of acute or chronic altitude exposure on patients with pre existing kidney diseases. Little is known however, about whether short or long duration high altitude exposure possesses a risk in this patient population. Given that many area of the kidney are marginally oxygenated even at the sea level and

that kidney disease may result in further renal hypoxia and hypoxia-associated renal injury, there is concern that high altitude may accelerate the progression of chronic kidney disease. Because renal insufficiency impaired urinary concentration and dilution capacity, there could be an increase risk for either volume depletion or overload. Although there is no direct evidence of impaired diuretic responses to hypoxia in patient with CKD, there is some evidence that hemodialysis patients may be at increased risk for volume overload, which may predispose to pulmonary edema and greater arterial hypoxemia. As a result of impaired erythropoietin production and shortened red cell survival, patients with CKD do not have the expected erythropoietic response to high altitude and show little to no changes in hemoglobin concentration. Last, patients with CKD often have co existing cardiovascular diseases from comorbidities such as diabetes and hypertension, which put them as risk for cardiac complication at high altitude (Yao Q,2004)

(1.3.6) **Chronic hypoxia and renal injury:**

Recent studies emphasize there role of chronic hypoxia in the tubulo interstitium as a final common pathway to end stage renal failure. When advanced, tubulo interstitial damage is associated with the loss of peritubular capillaries. Associated interstitial fibrosis impairs oxygen diffusion and supply to tubular and interstitial cell. Hypoxia of

tubular cells leads to apoptosis. This in turn exacerbates fibrosis of the kidney and subsequent chronic hypoxia, setting in train a vicious cycle whose end point is end stage renal failure (ESRD). A number of mechanisms that include tubulointerstitial hypoxia at an early stage have been identified. Glomenular injury and vasoconstriction of efferent arterioles as a result of imbalances in vasoactive substances decrease post glomenular peritubular capillary blood flow. Angiotensin II not only constricts efferent arterioles, but via its induction of oxidative stress, also hampers the efficient utilization of oxygen in tubular cells. Relative hypoxia in the kidney also results from increased metabolic demand in tubular cells. Furthermore, renal anemia hinders oxygen delivery. These factors can affect the kidney before the appearance of significant pathogenic changes in the vasculature and predispose the kidney to tubulointerstitial injury.

Therapeutic approaches that target the chronic hypoxia should prove effective against abroad range of renal disease. Current modalities include the improvement of anemia with erythropoietin, the preservation of peritubular capillary blood flow by blockade of rennin angiotensin system, and the use of anti oxidant.(Masaomi,2005)

(1.3.7) **Effect of high altitude on cardiovascular system:**

Altitude exposure is associated with major changes in cardiovascular function. The initial cardiovascular response to altitude

is characterized by an increase in cardiac output with tachycardia, no change in stroke volume, where blood pressure slightly increased. After few days of acclimatization, cardiac output returns to normal, but heart rate remains increased, so that stroke volume is decreased. Pulmonary artery pressure increases and ventricular function is maintained, with initially increased systolic function and altered diastolic patterns. Additional changes with acute altitude exposure include alteration in regional blood flow. Vasoconstriction occurs in the muscles, skin and viscera, while coronary vasodilatation and increased coronary blood flow occurs.(Maeije,2010).

The following are also cardiovascular changes in high altitude residences:

(1.3.7.1) Hematological changes:

No less important than the transport system is the transport vehicle, namely the RBC. During the first 1-2 weeks at high altitude, plasma volume decreases, raising the hemoglobin concentration by 1-2 g/dl. In addition, within hours of exposure to altitude, RBC production increases because production of erythropoietin is heightened. However, the overall response is slow, taking months to reach equilibrium.

The degree of Polycythemia is directly related to the altitude, up to an elevation of 3660m (12,000ft). Above this altitude, the hemoglobin concentration increases rapidly. However, if the systemic arterial

saturation falls below 60%, erythropoietin activity decreases. In subject living at 4540m (14,900ft), total blood volume gradually rises from 80 to nearly 100ml/kg, a change that represent an increase in RBC volume as plasma volume decreases.(Poothrukovil,2010)|

Polycythemia is associated with hyper viscosity and a decline in oxygen transport. An additional rise in hemoglobin concentration is observed with age at high altitude. At high altitude, climbers with Polycythemia have reduced maximal oxygen consumption, even when the breathe 100% oxygen. This observation suggests that the peripheral extraction of oxygen from blood is limited by its reduced flow. Phlebotomy and hemo dilution experiments in mountain climbers and autologous RBC transfusion in the athletes have not yielded information about the ideal hematocrit for any given altitude.

Platelet count decreases by 7% after two days at 5370m (17,600ft). Some suggest that exposure to high altitude induces hypercoagulable state in humans. Increased fibrinogen levels and a decreased clot lysis time were noted in 38 soldiers living at high altitude for 2 years, as compared with central subject at sea level. Soldiers with clinical evidence of pulmonary artery hypertension had somewhat low level of fibrinogen high level of platelet III and increased platelet adhesiveness. This evidence suggests that conversion to fibrin, and possiblely platelet deposition, were occurring in these subjects with pulmonary hypertension. Similar studies of the coagulation status of patients with

cyanotic congenital heart disease have been conducted. (Poothrukovil,2010)

(1.3.7.2) Pulmonary artery changes:

Pulmonary artery pressure is inversely dependent on a person's age and on environment. At sea level pulmonary artery pressure rapidly decrease from the systemic level of the fetus to near- adult level in the first hours or days after birth. However the decrease in pulmonary artery pressure in infants born at high altitude is both slower and smaller than the decline just described. In the Leadville, Colorad (3100m-10,200ft), the mean pulmonary artery pressure in healthy high school student was 25mm/Hg. Increasing to 54mm/Hg after exercise. These values were similar to those found in adults during operation Everest at a simulated altitude of (8840m) in a hypobaric chamber. Pulmonary artery pressure at low altitude such as Denver, Colorada (1610m-5280ft) are near values at sea level. Therefore, a critical partial pressure of oxygen appears to mark the level of hypoxia necessary to maintain pulmonary vasoconstriction.

A recently published study on children in Tibet (3600m), showed significant elevated pulmonary hypertension measured by Doppler Ultrasound and ECG.

Noninvasive and invasive evaluation of pulmonary arterial pressure were compared in a separate study from Kyrgyzstan et.al. A

combination of ECG and Doppler measurement was found to correlate with cardiac catheterization data. Pulmonary flow acceleration time was found to be a good predictor of pulmonary hypertension. (Poothrukovil,2010)

1.4 Problem of the study:

The normal size of a kidney is variable and can provide a rough indications of renal function. Decrease or increase in renal size is an indication of many renal diseases. In order to estimate renal size, normal values must established first. Aseer region is considered to be one of high altitude areas in Kingdom of Saudi Arabia (2200m) and as far we know, these are no reliable reference tables for kidney size and volume for population living in this area. The prevalence of hypertension among people living in high altitude was found to be high compared to people living in low altitude (Brito,2007) .These are also no reference values for renal size and volume for hypertension patients in high altitude area. Not many studies have been done to evaluate the progression of hypertension in high altitude and its effect on kidneys.

1.5 Objectives of the study:

The main objective of the study was to evaluate renal size and volume for patients living in high altitude area by using ultrasonography in order to obtain a reference index.

specific objectives are

(i) To measure renal size and volume for normal population living in high altitude by using ultrasound.

(ii) To estimate renal size and volume for hypertensive patients living in high altitude by using ultrasound.

(iii) To compare renal size of normal population living in high altitude with the renal size of people living in low altitude.

(iv) To establish a reference table for renal size and volume for hypertensive and normal population.

(v) To find the incidence of renal artery stenosis (RAS) among hypertensive patients living in high altitude by using Doppler ultrasound.

(vi) To find the significance of exrtarenal Doppler parameters in detecting (RAS)

(vii) To estimate (RAS) progression for hypertensive patients living in high altitude.

(viii) To measure renal volume of (RAS) patients and compare it with hypertensive patients without (RAS).

1.6 significance of the study :

This study will establish reference values for normal populations and hypertensive patients living at high altitude. It will also show the importance of volume measurement in routine evaluation and monitoring of kidney diseases for people living in high altitude. The study will improve gray scale ultrasound parameters as a first step in detecting the cause of hypertension for people living in high altitude. The study will also establish reference values for extra renal Doppler parameters and show the usefulness of these parameters rather than intra renal in detecting renal artery stenosis.

1.7 Outline of the study:

This study was organized into five chapters , where chapter one is introduction including anatomy, physiology and patho physiology of the kidney, the pathology of hypertension and patho physiology of high altitude area. Secondly chapter two include ultrasound and previous studies. Chapter three describes methods and techniques of gray scale and Doppler ultrasound examination for normal and hypertensive patients. It also provides an outline of equipments used in the study. Chapter four deals with the results of the usage of gray scale and

Doppler ultrasound in detecting renal artery stenosis among hypertensive patients. This chapter also contains the results of renal size measurements for normal populations in high altitude. Chapter five includes discussion of applying gray scale and Doppler ultrasound parameters for both normal and hypertensive patients. The chapter also contains conclusion, recommendation and future work

Chapter two

Literature review

(2.1): Renal ultrasonography

(2.1.1): Gray scale ultrasound scanning

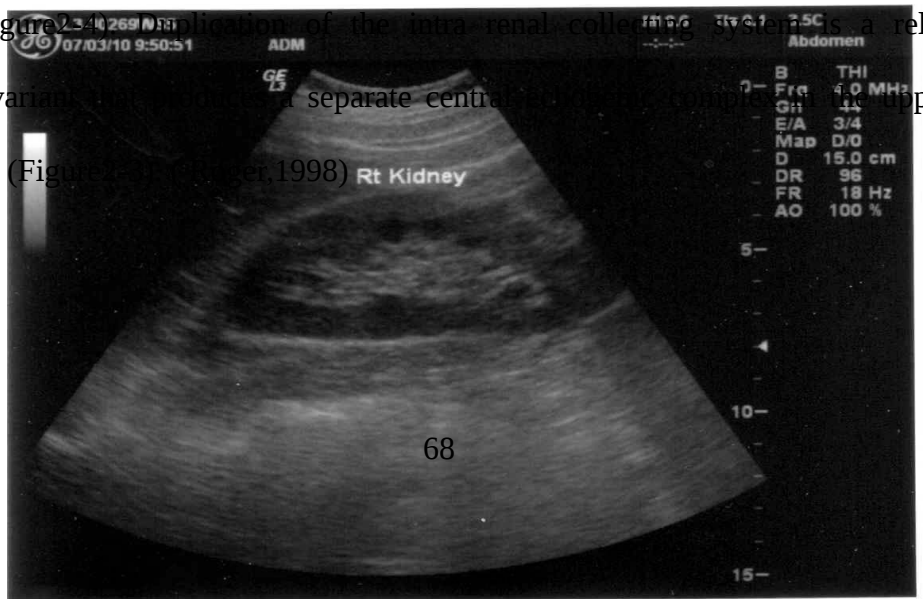
(2.1.1.1): Introduction

The application of the ultrasound to medical diagnosis has seen continuous development and growth over several decades. Early primitive display modes, such as A-mode and static B-mode, borrowed from metallurgical testing and radar technologies of the time, have given way to high performance, real time imaging. Modern ultrasound systems do much more than produce image of unborn babies, however, The Doppler effect is used to study motion within the body, particularly that of blood. Modern ultrasound systems are able to make detailed measurements of blood movements in blood vessels as well as show moving two dimensional (2D) images of flow patterns. In many areas, ultrasound is now chosen as the first line of investigation, before alternative imaging techniques. B-mode ultrasound image is a cross-sectional image representing tissues and organ boundaries within the body. It is constructed from the echoes, which are generated by reflection of ultrasound waves at tissue boundaries, and scattering from small irregularities within tissue. Each echo is displayed at a point in the image, which corresponds to the relative position of its origin within the body cross section, resulting in a scaled map of echo producing features. The brightness of the image at each point is related to the strength or amplitude of the echo, giving rise to the term B-mode or brightness mode.(Frederick,2006)

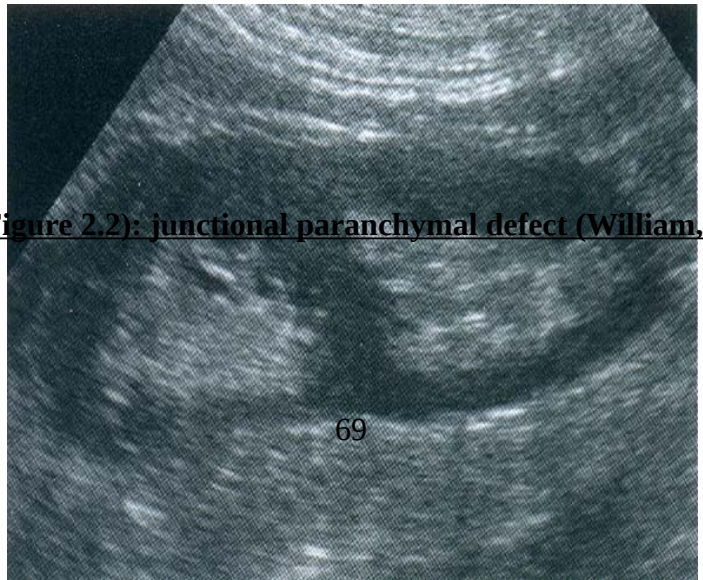
(2.1.1.2): Normal sonographic anatomy:

As it mentioned before, the kidneys have a very complex internal architecture that is responsible for producing a variety of internal echogenicities. The central renal sinuses are composed of fibro fatty tissues that appear echogenic on sonogram. The renal vessel and collecting system are occasionally seen as thin anechoic, fluid containing structures, located within the echogenic tissues of the renal sinus. Sonographically, the pyramids are cone or heart shaped hypo echoic structure (Figure 2-1). The cortex is slightly more echogenic that the pyramids, although this distinction is not always apparent. The cortical echogenicity of the kidney should be equal or slightly less than the liver and less than that of the spleen. The kidneys appear sonographically avoid in cross section, with the longest dimension directed from arteriomedial to posteriolateral. Therefore, longitudinal views of the kidney will demonstrate a different shape depending on how the view was obtained.

The external countour of the kidney is generally smooth. A common normal variant called the junctional paranchymal defect produces a wedge-shaped hyper echoic defect in the anterior aspect of the kidney near the junction of the upper and middle thirds. It can be distinguished from a scar or mass by its typical triangular shape and location (Figure2-2). A prominent column of cortical tissue occasionally protrudes into the renal sinus and can simulate a mass. These are called columns of Bertin and are located in the mid third of the kidney. They have similar echogenicity to the rest of the cortex (Figure2-3). Duplication of the intra renal collecting system is a relatively common variant that produces a separate central collecting complex in the upper and lower pole (Figure2-4) (Grainger,1998)

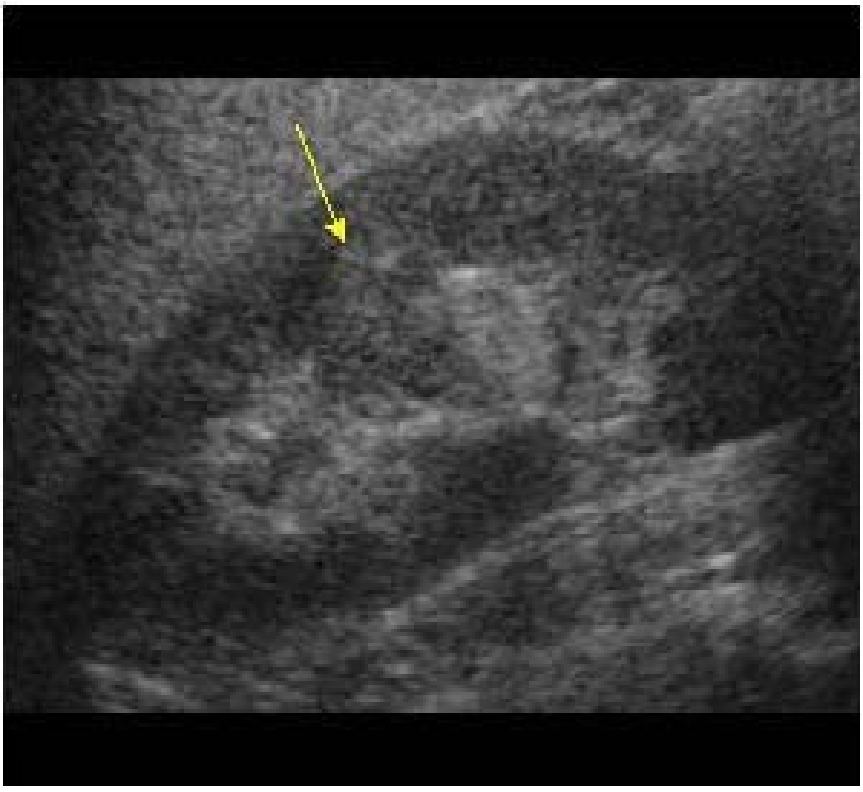


(Figure 2.1): normal kidney (Roger,1998)



(Figure 2.2): junctional paranchymal defect (William,2004)

(Figure 2.3): duplication of intrarenal collecting system (William, 2004)



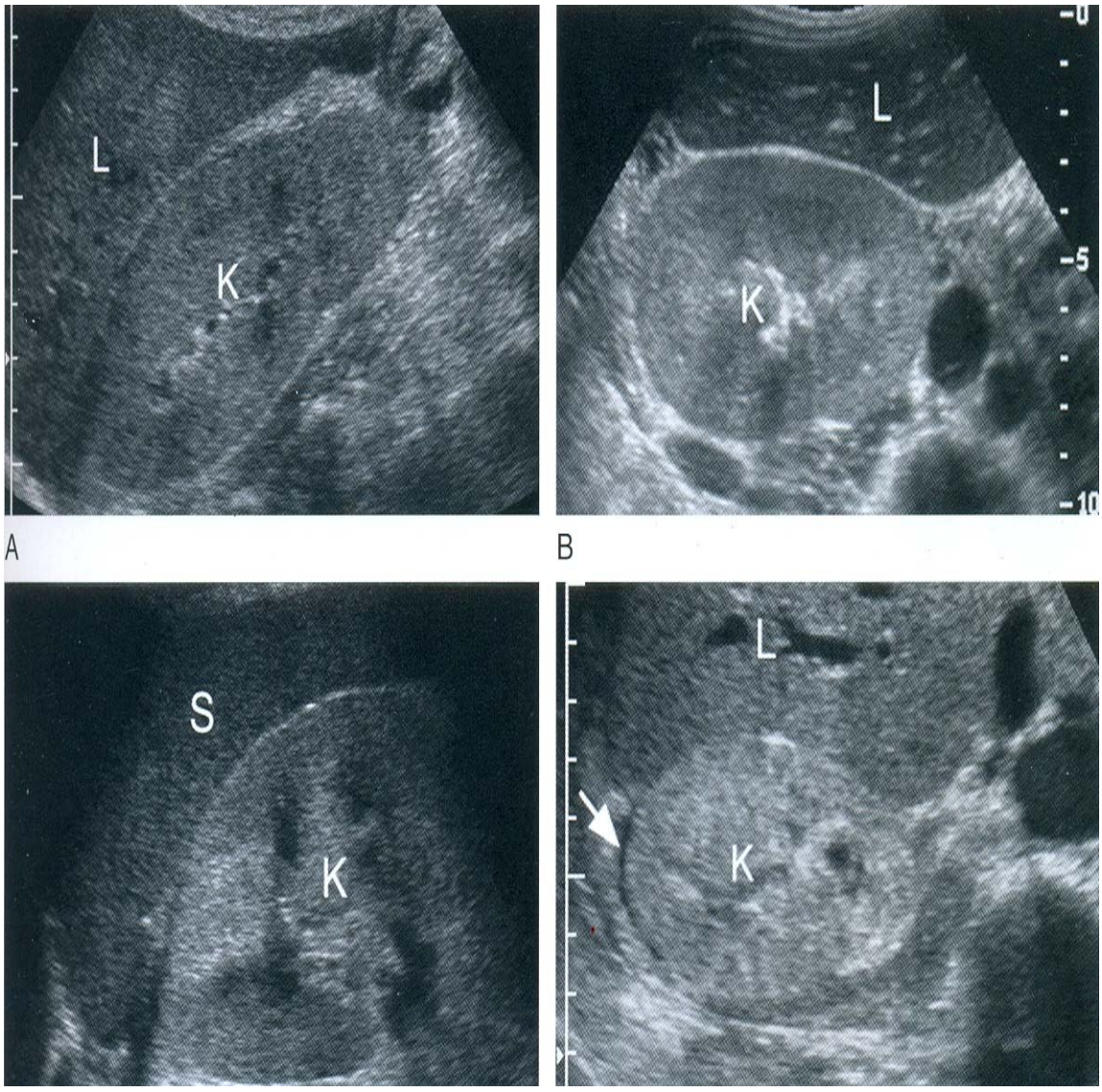
Figure(2.4): Colum of Bertin (Palmer,1995)

(2.1.1.3): Protocol of scanning:

The native kidneys are best imaged with a 2 to 5 MHZ transducer, depending on the patient's body habitués and the depth of the kidney. Sector type probes or curved arrays are generally best for imaging the kidneys. The kidneys can be viewed from a variety of approaches. The upper poles of each kidney are often seen best with the patient supine and using a high, posterior, intercostals approach and the liver or spleen as acoustic window. Failure to go high enough or posterior enough is the most common reason for inadequate visualization of the upper pole, especially on the left. The lower poles can be seen using a sub costal approach, usually during deep inspiration. The transducer location should be varied from anterior to lateral to posterior, and the patient position should be varied from supine to decubitus until the best view is obtained. In some people the lower pole of the left kidney can be seen best from an anterolateral approach with the patient in a right lateral decubitus position. This view seems to be especially advantageous in obese patients. It is important to compare renal echogenicity to the liver and spleen. This allows for detection of abnormally echogenic kidneys, as well as abnormalities in hepatic and splenic echogenicity. Therefore views including a portion of the liver and spleen are important to obtain. It is equally important to visualize the kidneys from a posterior or posteriolateral approach without using the liver or spleen as acoustic window. A posterior approach usually gets the transducer closer to the kidney and often will allow for better visualization of common abnormalities such as cyst or stone (Mike,2001 and Palmer,1995)

(2.1.1.4): Ultrasound appearance of renal parenchymal disease:

A large number of diseases affect the renal parenchyma and produce renal failure. The term “medical renal disease” is often used but is not truly appropriate because some of the patients will benefit from a surgical procedure (renal transplantation). Increased paranchymal echogenicity is often seen in the setting of renal parachymal disease. The degree of echogenicity correlates loosely with the severity of, but not the type of histopathological changes. Therefore, although an underlying paranchymal abnormality is suggested by increased echogenicity, the cause can not be determined. Echogenicity is considered increased when the right kidney is more echogenic than the liver or when the echogenicity of the left kidney is equal or greater than that of the spleen (Figure2-5) . If images are not available to show the relative echogenicity of the kidneys and the liver or spleen, echogenicity is considered increased, if the pyramids are unusually hypo echoic with respect to the renal cortex. In most cased, patients with paranchymal disease are scanned because of acute renal failure. In this setting, it is not uncommon to see a trace amount of perinephric fluids, and this should not be misinterpreted as a sign of infection or trauma. The main role of sonography in these patients is to exclude urinary obstruction and determines renal size. Renal biopsy of normal sized or enlarge kidney may then be done to determine the underlying histologic diagnosis. Small kidneys usually indicate a chronic process with end-stage changes, and biopsy is often not indicated because the histopathologic finding cannot distinguish the possible cause. (William,2004)



(Figure 2.5): renal paranchmal disease (William,2004)

(2.1.2): Doppler ultrasound for kidney:

(2.1.2.1); Introduction

Color duplex scanning has added an important dimension to renal ultrasound studies. It can provide conclusive evidence of renal artery stenos is (RAs), and examiners need no longer be content with offering a diagnose of “vascular atrophy kidney”. Doppler ultrasound can detect pathologic changes even before they have led to structural tissue alteration.

Renal allograft can be visualized particularly well with owing to their superficial location in the iliac fosse. Allograft rejection can be detected at an early stage, and problems with the graft artery and principle veins can be accurately diagnosed. Color duplex scanning can replace practically all radionuclide and angiographic studies in renal allograft evaluation.(Mathias,2001)

(2.1.2.2): Adjusting Doppler parameters:

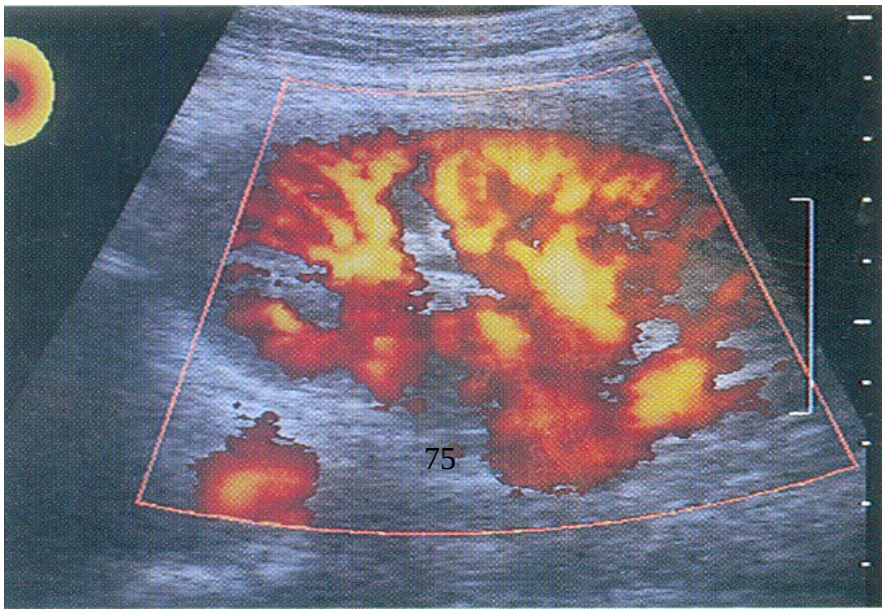
Throughout the course of examination of the renal artery, color Doppler is frequently switched on to confirm the nature and direction of flow. The optimum pulse repetition frequency (PRF) is selected to detect moderate flow velocities, although it may need to be modified to detect high velocities if a stenos is with aliasing of the color signal is present. For spectral Doppler, the sample volume is placed on the selected vessel shown on the color display. Recording spectral Doppler is better performed in duplex rather than triplex mode, since the processing required for triplex imaging reduces both the frame rate and pulse repetition frequency, compromising further the discrimination of high velocity signals at depth.(Hoskins,2003)

Color Doppler is invaluable in the assessment of intra renal vessels. With the system set to detect low or moderate velocities, flow can be identified in almost all

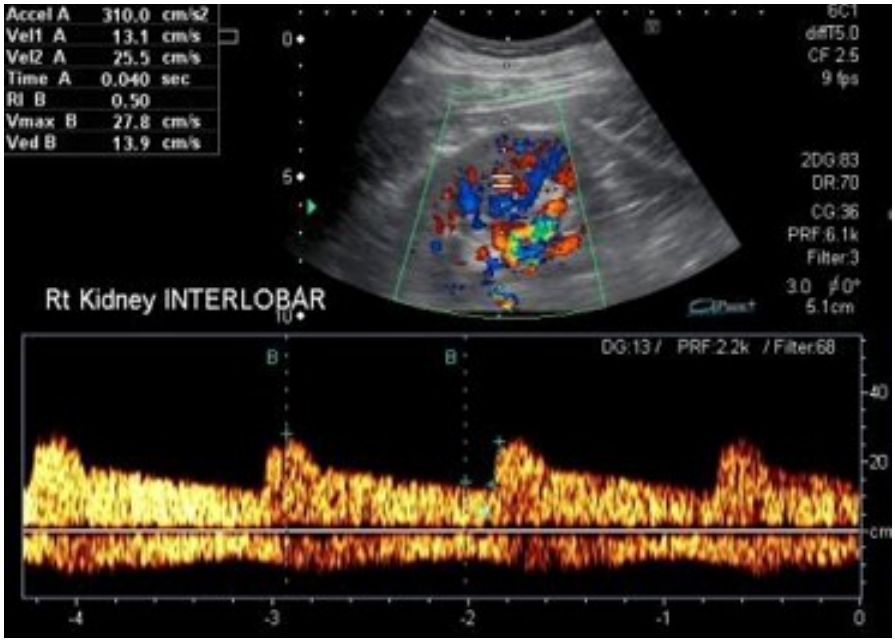
patients in the vessels at the renal hilum, particularly if the angle of incidence is optimized to achieve angle of less than 60 degree relative to the course of the vessels. Angling the probe medially from the right or left flank will allow assessment of the intra renal vessels. Peripheral smaller vessels are usually better demonstrated with power Doppler although in this situation the directional information is lost (Figure2-6).

Evaluation of global blood flow required that the color box be opened to its fullness extend in order to visualize relative blood flow distribution (Figure2-7). This is also important in the evaluation of renal tumors so that flow in the lesion can be compared with that in normal adjacent renal tissues. However, this compromises temporal resolution with lower frame rates and pulse repetition frequency, the size of the color box should be minimized prior to spectral sampling (Figure2-8).

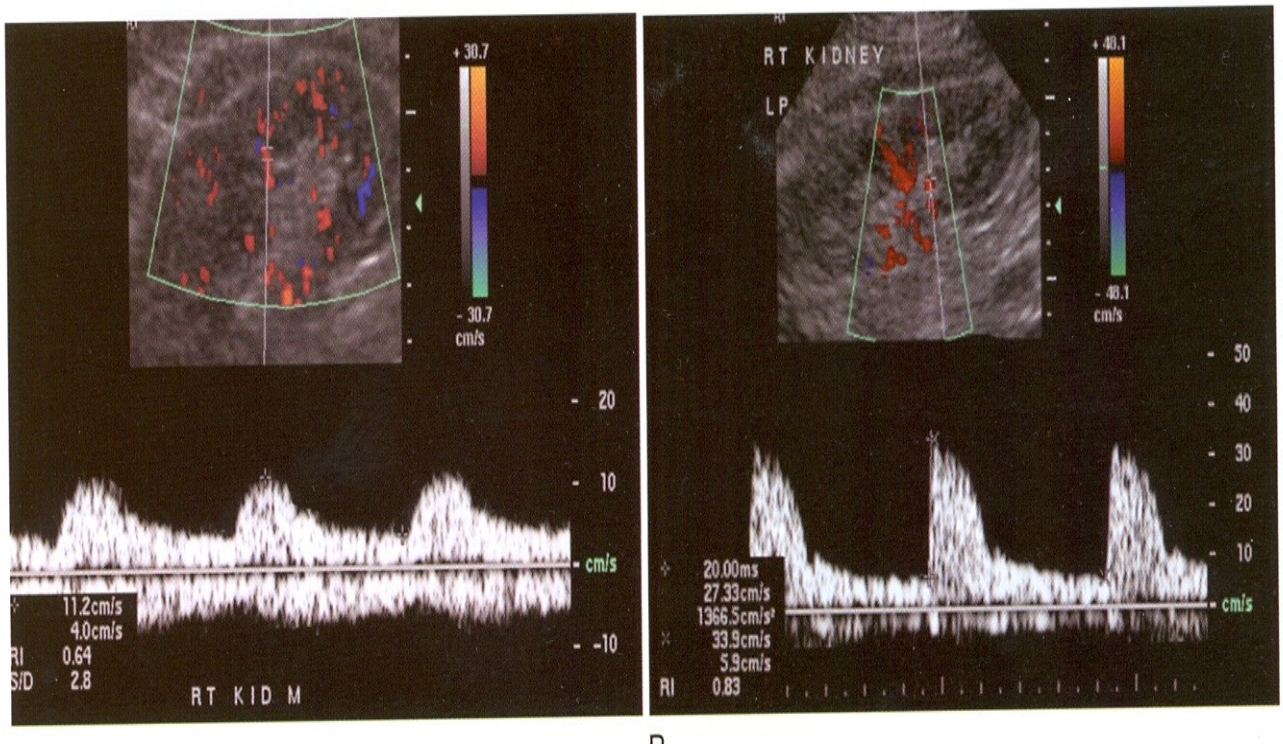
It is frequently value to activate the zoom function on the machine prior to interrogation with color Doppler, as this allows for greater sensitivity of color signal recording within the intra renal vessels. Using this technique, the hilar and interlobular vessels are demonstrated in all patients, although arcuate and striate arteries are only seen in similar patients. In case of the arcuate vessels, this is partly due to their course, which is usually at right angel to the incident beam. Advances in technology have widened the group in whom the entire renovascular pattern can be identified (Paul,2000)



(Figure 2.6): power Doppler (Paul,2000)



Figure(2.7) : Distribution of blood flow inside the kidney (Mike,2001)



A B

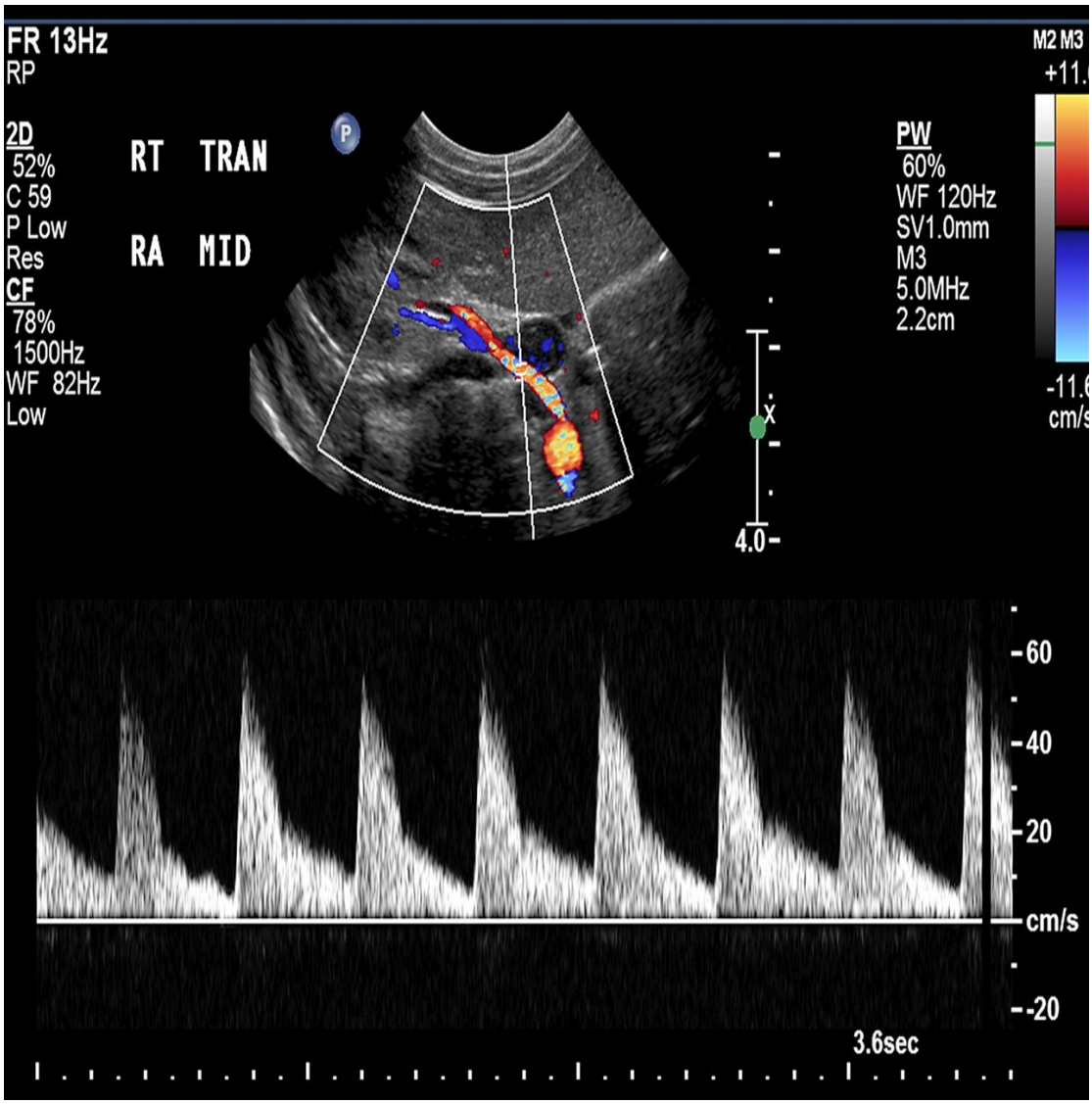
Figure(2.8) : Changes in the spectrum by (A) maximizing the color box and (B) minimizing the color box. (Rumwell,2009)

(2.1.2.3): Patient preparation and transducer position:

The patient is examined in a fasting state. Because the renal arteries are deeply situated, we use a low-frequency transducer operating at 2 to 3.5 MHZ. The right renal artery branches from the aorta at about the 10 o'clock position, arising slightly below the origin of the superior mesenteric artery (Figure2-9) . It curves posteriorly and pass behind the inferior vena cava on its way to the renal hilum. The left renal artery arises from the aorta at about the 4 o'clock position, usually on the same level as the right artery. It can be traced for approximately 3cm from the aorta to the hilum. It is more difficult to visualize than the right renal artery, as it is more frequently obscured by gas in overlying loops of small bowel.

Angle correction velocity measurements are taken at five points along the course of the main renal arteries. Normal peak velocity range from 50 to 160 m/s.

The renal arteries can be visualized in an oblique coronal longitudinal section with the transducer placed on the right mid clavicular line, or they can be imaged in an abdominal transverse section. The best view is obtained by positioning the transducer just above the midway point between the xiphoid process and the umbilicus. If bowel gases obscure visualization of the aorta at this location move the transducer up to the subxiphoid level and angle it downwards, or scan from a more caudal level and angle the transducer upward. The best acoustic window will vary depending on the bowel gas distribution at the time of examination (Satish,2000)



Figure(2.9) : Doppler ultrasound of the Rt renal artery (Matthias,2001)

(2.1.2.4): Examination technique and normal findings:

When the origin of the renal artery is imaged with color flow, it is common to find an area of color inversion in the curved vessel (Figure2-10) . The relatively the dark color shades distinguish this normal phenomenon from the bright color shift that is caused by aliasing due to proximal renal artery stenosis. (Figure2-11) Show the normal left renal artery arising from the aorta anterior to the vertebral column. Oblique coronal longitudinal scans are obtained in the left lateral dicubitus position for the right renal artery. The transducer is oriented longitudinally and placed in the mid clavicular line (Figure2-12). It is angled until the vena cava is demonstrated in longitudinal section. If bowel gases obscure visualization, the transducer should be moved over the skin and angled accordingly until a satisfactory acoustic window is found. The aorta is visualized behind the vena cava. The right renal artery passes directly toward the transducer from the aorta. The flow directly towards the transducer produces a large Doppler frequency shift, yielding conspicuous color flow and a well defined Doppler spectrum. The left renal artery courses a way from the transducer. This projection of the renal arteries is best for determining whether one or more polar arteries are presented. (Figure2-13) (Paul,2000)

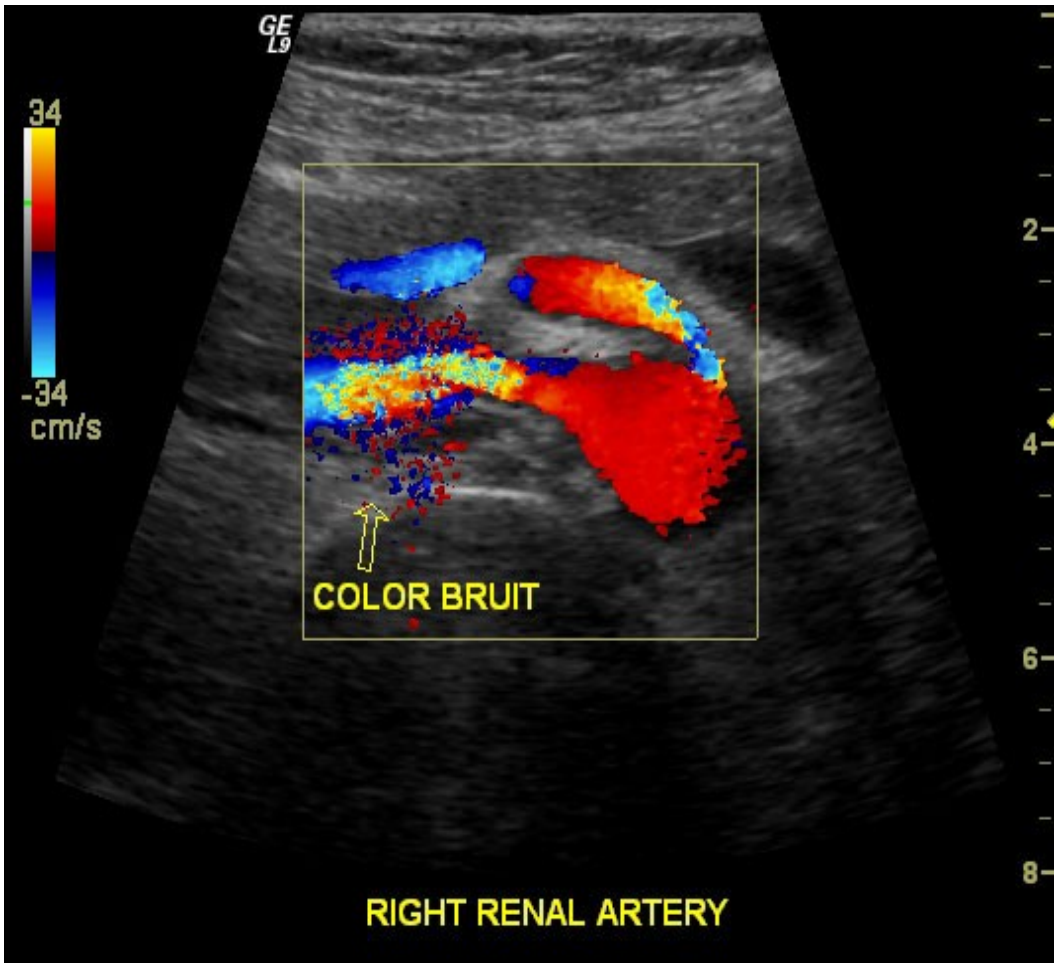


Figure (2.10): Area of color inversion and aliasing due to proximal (RAS)

(Matthias,2001)

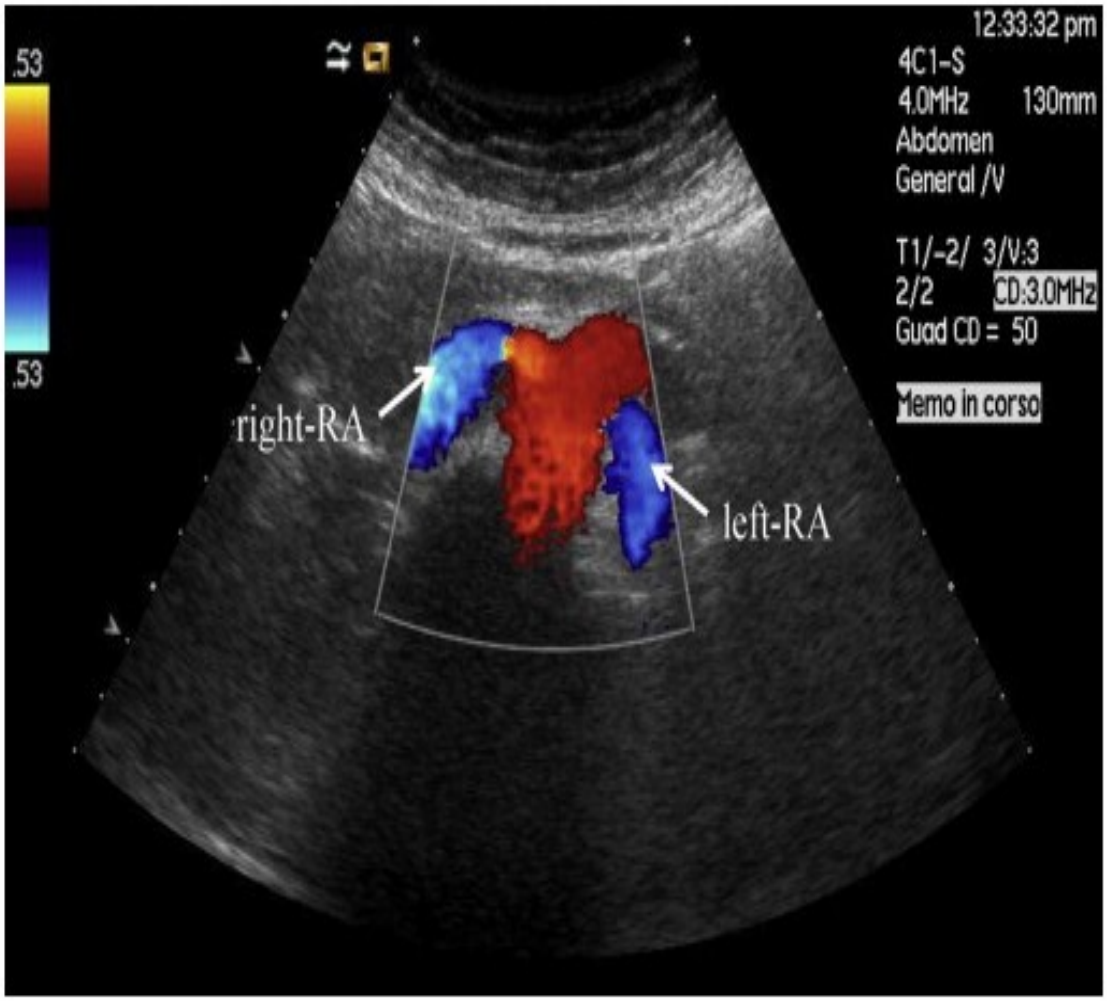


Fig. 2. Axial section of the midepigastric region showing the origin of both RAs.

Figure(2.11) : Dark color shades in both renal arteries (Rumwell,2009)

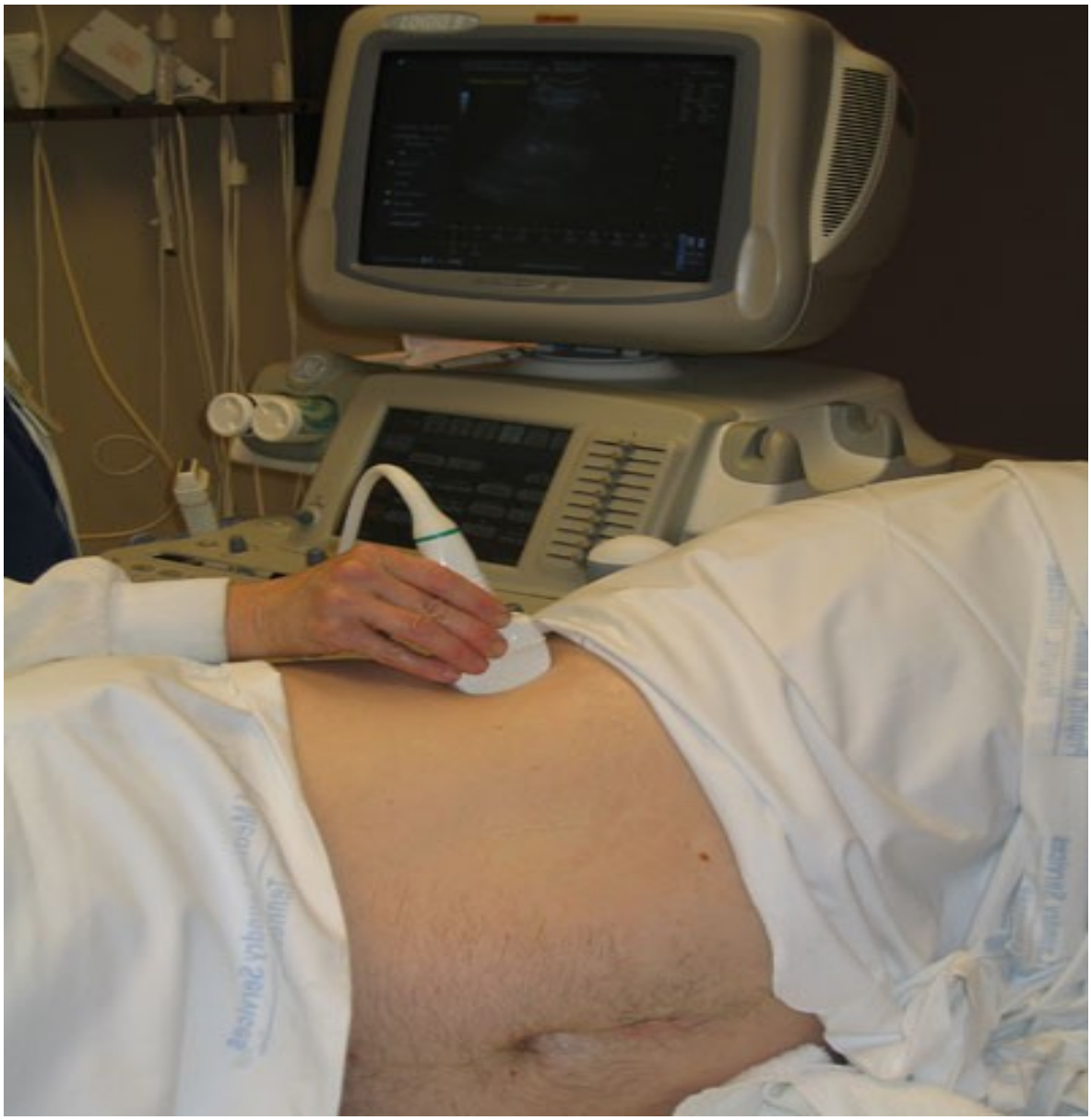
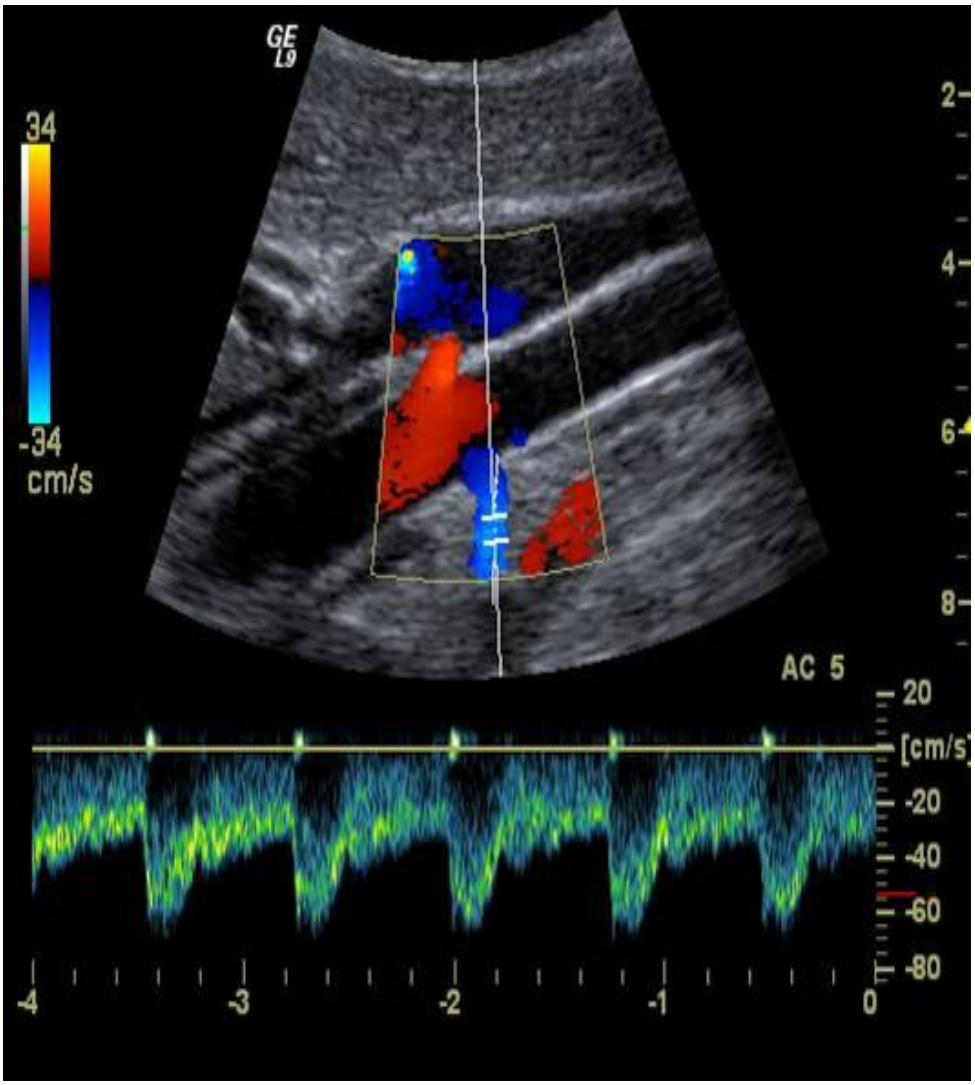


Figure (2.12) : Longitudinal scanning of renal artery by placing the probe in the midclavicular line (Coombs,2002)

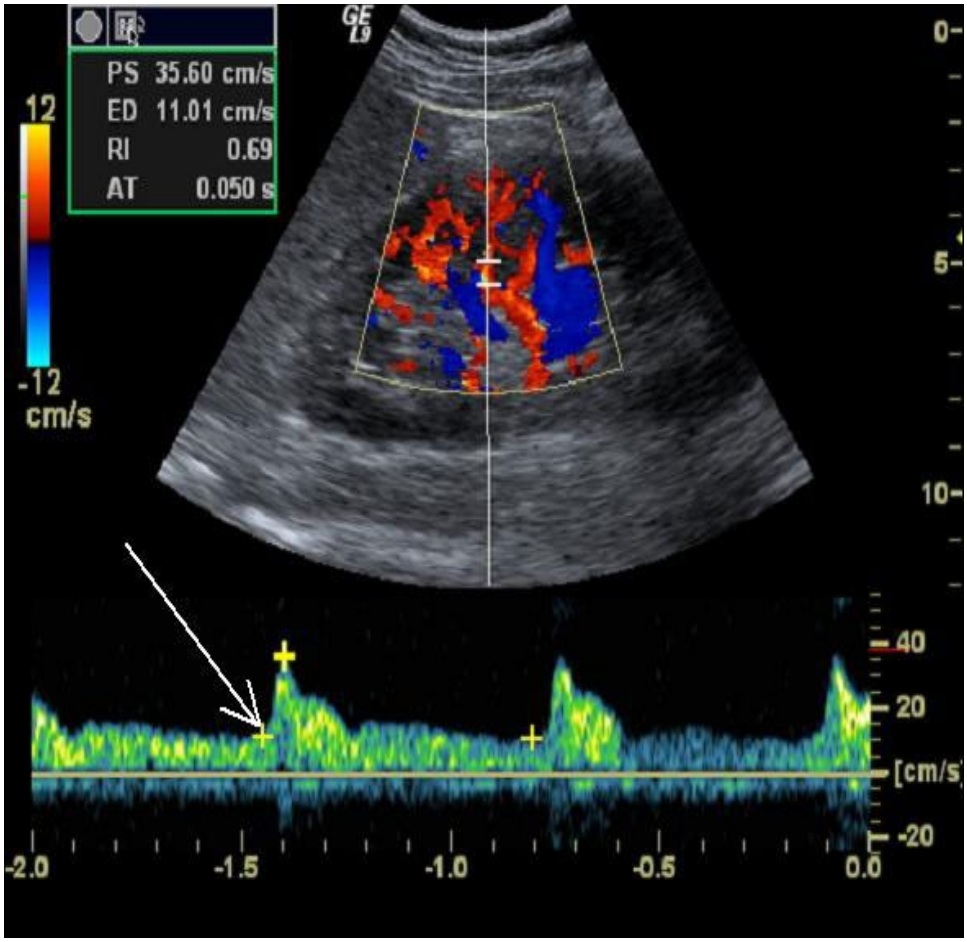


Figure(2.13) : Left renal artery courses away from the transducer. (Hun,2000)

(2.1.2.5): The intra renal vessels:

First the kidneys are optimally visualized in the B-mode image in the left and right lateral decubitus position. This can also be done in a standard supine position in most patients. After obtaining an optimum B-mode view, activation of colour flow imaging and spectral analysis will take place.

Demonstration of the anatomical location and course of the intra renal vessels is almost exclusively restricted to color Doppler, although pulsation can be seen on real time at the site of the interlobar vessels, and occasionally at the bright reflectors at the corticomedullary margin which represent the arcuate vessels. The arteries are each accompanied by vein; they divided into branches to the upper and lower poles and to the anterior and posterior parenchyma (Figure2-14). The interlobar vessels course into the renal parenchyma on either side of the renal papillae, giving tiny invisible branches to the medulla as the arcuate arteries, giving off multiple small striate branches which extend out towards the cortex. With more modern and sensitive machines, the capsular artery can occasionally be demonstrated at the margin of the kidneys curving around the surface. (Matthias,2001)



Figure(2.14) :Doppler ultrasound for intrarenal blood vessels (Matthias,2001)

(2.1.2.6): Characteristic of Doppler spectrum:

The main purpose of the Doppler spectrum is to measure the velocity of the blood. The Doppler spectrum of the renal arteries is bi phase, consisting of systolic and diastolic phase. A typical spectrum from the renal arteries is shown in (Figure2-15) . There is a rapid systolic upstroke, which is occasionally followed by a secondary slower rise to peak systole (although this is more frequently seen with advance age and hypertension). There is subsequently a gradual diastolic decay but with persistent forward flow in diastole. The spectral window should also be clear for normal arteries.

Renal vein spectra are different from right and left veins (Figure2-16). The right renal vein is short and often therefore mirrors the pulsatility of the inferior vena cava, while the left, particularly if it is sampled to the left of the superior mesenteric artery, may show only slight variability of flow velocities consequent upon cardiac and respiratory activity (Satish,2003)

(2.1.2.7): Indices used in the assessment of renal blood flow:

A multiplicity of indices is uses for evaluation of renal blood flow. The range indicates that no single index provides all the information that is necessary to adequate evaluation of renal pathophysiology. The indices used, together with normal values are shown in table (4-1), and some examples are shown in (Figure2-17).

Resistive index (RI) or pourcelot index is the most common type of index which is used in assessment of renal artery blood flow. It is independent of beam angle and it is described as peak systolic velocity minus end diastolic velocity divided by systolic velocity. (Barry,2006)

$$RI = \frac{S - D}{S}$$

S = Systolic velocity

D = Diastolic velocity

High resistant in the distal vessels, produce a low diastolic flow in the supplying artery and results in a high value for this index; a low resistance results in a low value as there is higher diastolic flow. In healthy subject, the (RI) values will show only minimal differences within one kidney and between the kidneys. A mean value is calculated from the resistance indices for each kidney. The (RI) values measurement in healthy subject show a significant dependence on age and the area sampled. The values in the main artery are higher in the hilar region (0.65 ± 0.7) than in the more distal smaller arteries and they are lowest in the interlobar arteries (0.54. ± 0.2). Comparable values are obtained only when arteries of equal order are sampled. The best sampling sites are the segmental and interlobar arteries, as these vessels are easy to fine at the junction of the renal pelvis and parenchyma. They usually pass directly towards the transducer and produce a high Doppler frequency shift, resulting in a good quality color flow and spectral images. (RI) values are also age dependant: they are higher in elderly patients. Renal blood flow is more pulsatile in older patients, so resistance increases due to interstitial fibrosis. (RI) values are also increases in hypertensive patients. This is presumably consequent upon the effect of Juxtaglomerular apparatus producing vasoconstriction, but also perhaps on the development of hypertensive nephro-sclenosis. A further cause of variability of

Doppler index (RI) related to acute renal failure, obstruction of renal pelvis, extra renal compression, bradycardia and acute rejection (Paul,2000) See (Table2-3).

Index	Range
Pulsalitily index (PI)	0.7 – 1.4
Recessive index (RI)	0.56 – 0.7
Peak systolic velocity (PSV)	60 – 140 cm/sec (< 180)
Diastolic/ Systolic rates (D/S)	0.26 – 0.4
Renal artery/Aorta ratio (RAR)	< 3.5
Acceleration time (AT)	42 – 57 ms
Acceleration index (AI)	250 – 380 cm/sec

Table (2-1): Normal renal artery Doppler indices (Paul,2000)

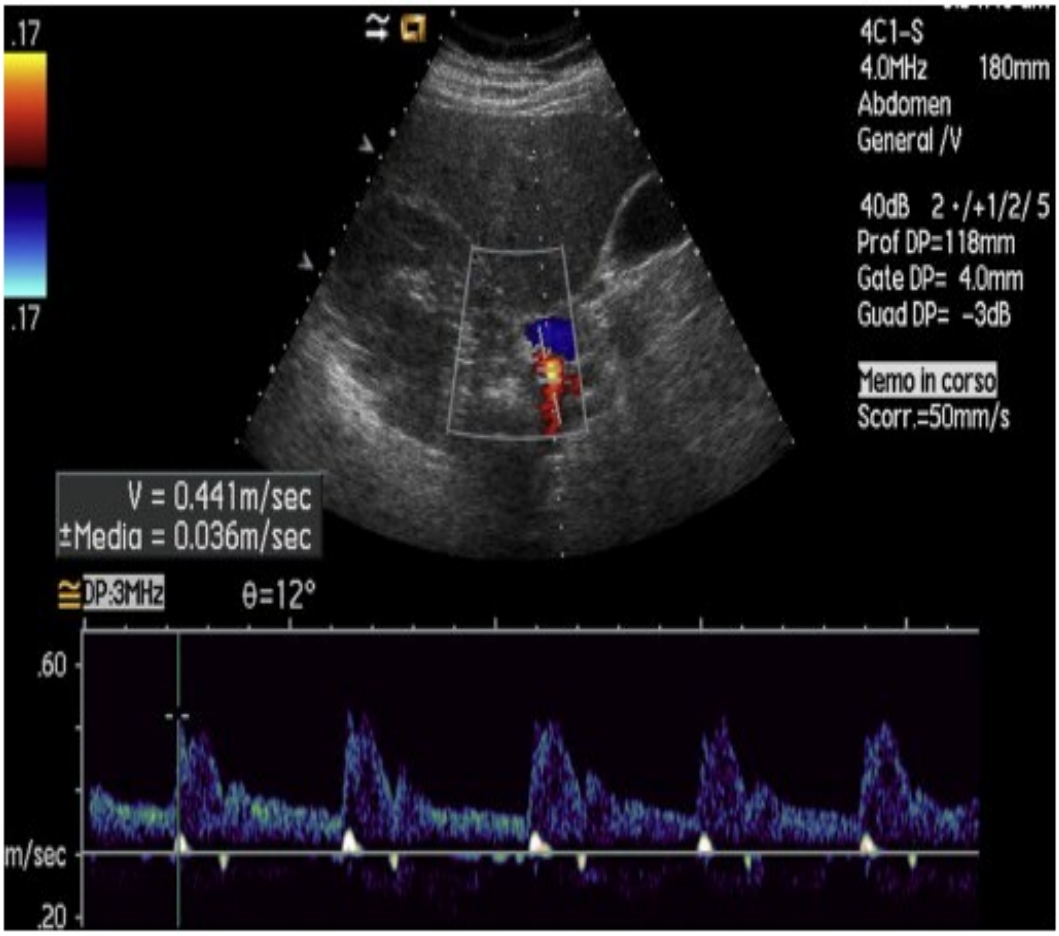
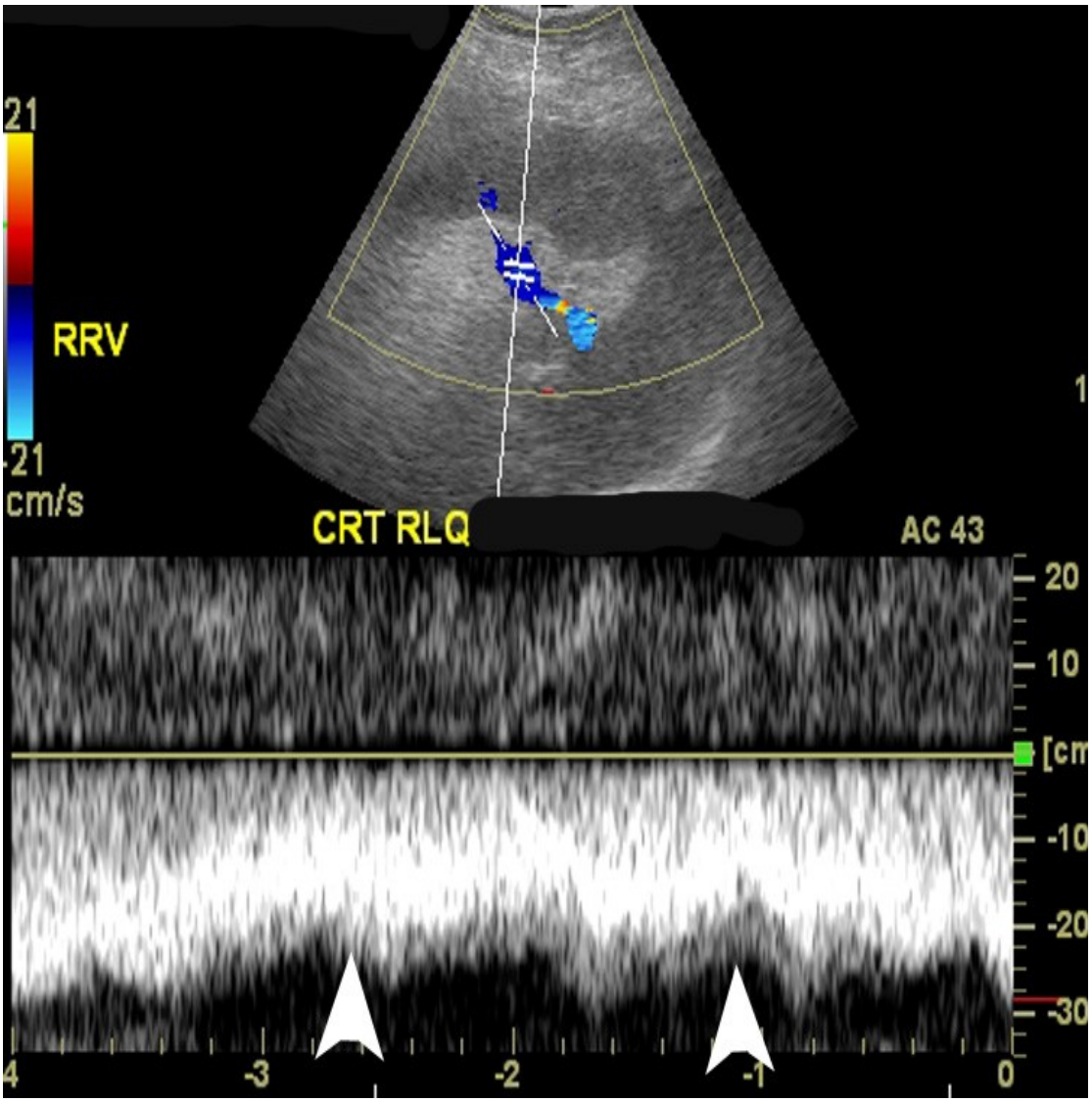
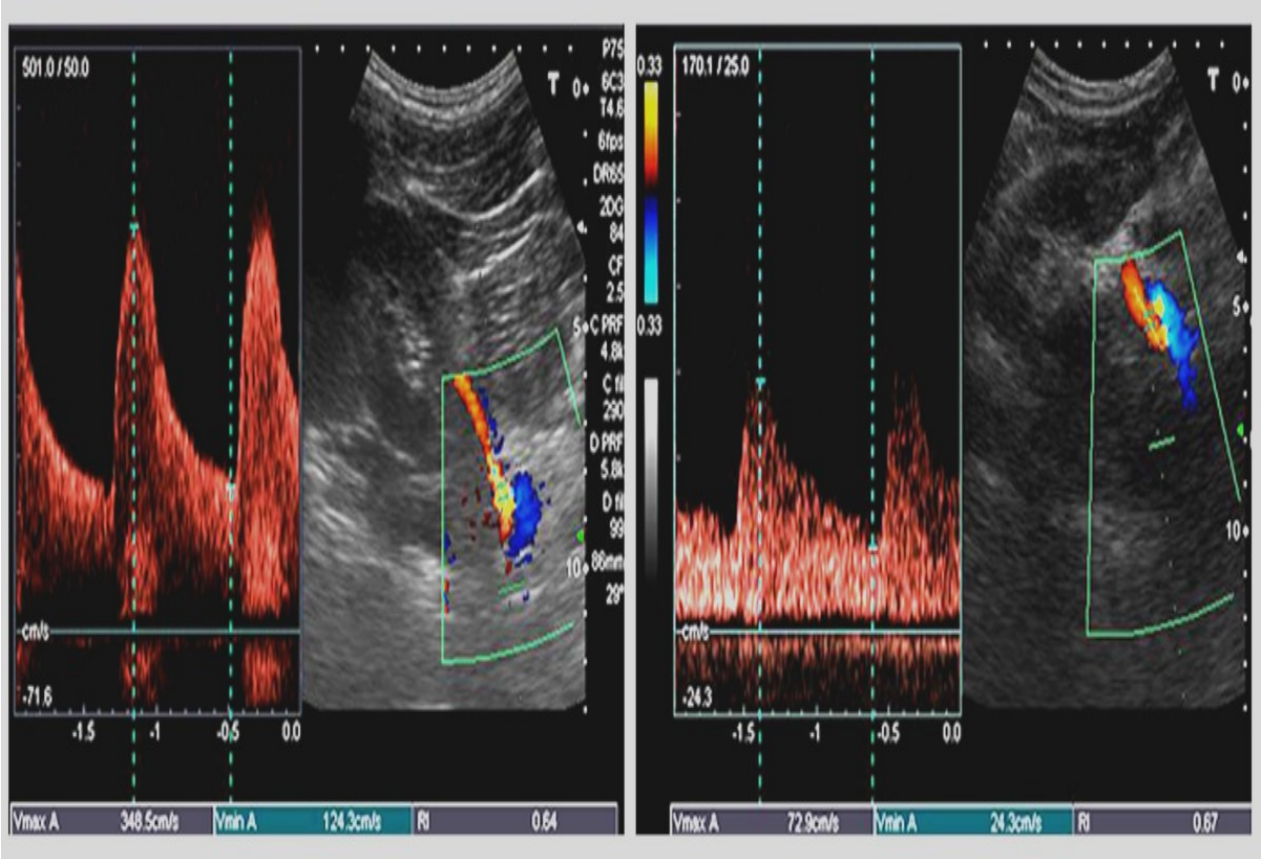


Fig. 5. Spectral Doppler US image of the right RA in a normal subject. Note the small spike occurring at the end of the systolic rise. This feature is seen only in a normal main RA.

Figure(2.15) : Normal Doppler spectrum of the renal artery Coombs,2002)



Figure(2.16): Normal Doppler spectrum of the renal vein (Coombs,2002)



Figure(2.17) : Measurement of Doppler indices (Satish,2003)

(2.1.3): Ultrasound diagnosis of (RAS):

Contrast angiography (CA) is the gold standard in the diagnose of (RAS). Due to its invasive nature, however (CA) is not suitable for screening. Multiple studies have shown that Doppler ultrasound can be an effective tool in the diagnose of (RAS). Both a direct (evaluation of the main renal artery) and indirect (evaluation of the segmental interlobar arteries) method of diagnosing (RAS) have been shown to be useful. Direct and indirect methods have been shown to have sensitivity and specificity in the low to mid 90% range. The most reliable approach combines the two methods. Other test used for detection of (RAS) includes radio nuclide scanning, MRI and spiral CT.

(2.1.3.1): Direct evaluation of the main renal artery:

The exam begins with imaging of the kidneys. The length of each kidney is measure and compared to the contra lateral kidney. The normal kidney measures from (8.5 – 13cm) in long axis. Differences greater than 2 cm in length between the kidneys is suggestive of renal artery occlusion on the side of the smaller kidney. Normal renal parenchyma measures greater than 1cm in thickness. The parenchyma surface should be smooth with an echogenicity equal to or slightly less than the normal liver parenchyma. The direct methods involve Doppler interrogation of the entire length of the main renal artery, including any accessory renal arteries. Although stenosis is usually located near the renal artery origin, fibro muscular dysplasia is more often located in the mid to distal segment, thus requiring a look at the entire length of each artery. Since stenosis in an accessory renal artery can cause renovascular hypertension it is important to search for and interrogate these vessels.

The highest velocity found in the renal artery is compared to that of the abdominal aorta (at the level of renal artery). This is termed renal aortic ratio (RAR). Color Doppler is useful to identify and map the main renal arteries and to locate accessory renal arteries. Doppler angle correction is more accurate with the use of color Doppler since visualization of the path of the renal vessels is improved. Velocities greater than 200 cm/s have been shown to indicate > 60% (RAS). Post stenotic turbulence must be documented beyond any focal velocity increase to confirm stenois. Bruits seen in color Doppler or in the spectral wave form can also increase diagnostic confidence and aid in localization of stenosis. The (RAR) is calculated by dividing the highest peak systolic velocity in the renal artery by the normal aortic velocity. A (RAR) greater than 3.5 is considered abnormal (Figure2-18).

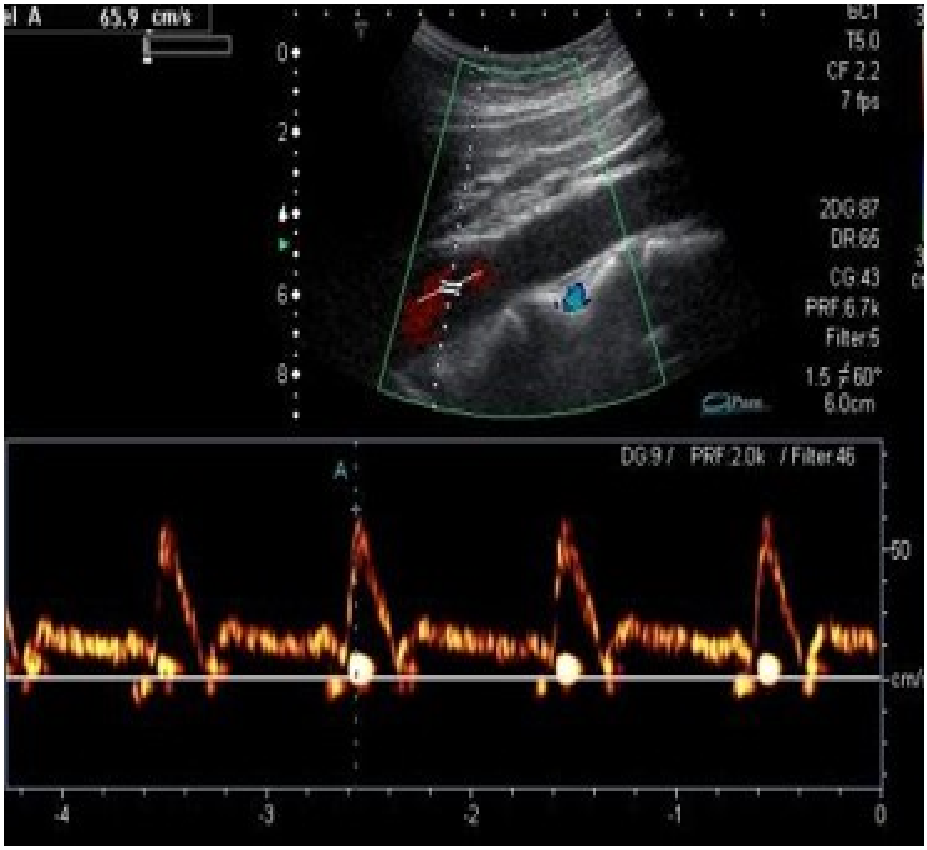
Attention to Doppler technique is key in this exam. The Doppler angle must be 60 degrees or less and aligned parallel to the vessel wall. Angle greater than 60 degrees tend to result in over estimation of the velocity. Misalignment of the angle correction cursor so that it is not parallel with the vessel wall, is a common cause of incorrect velocity measurements. The image is often frozen when obtaining Doppler reading duplex exams. If the probe position is adjusted to improve the Doppler trace while the image is frozen, the image is no longer accurately portrays the Doppler location and the angle may not be measured accurately. To avoid this pitfall, it is necessary to update the image after manipulating the probe. A low Doppler frequency is recommended (usually 2-3 MHZ) to reduce aliasing of the waveform and improve penetration. The system pulse repetition frequency (PRF) is monitored and increased whenever aliasing is encountered so that the systolic peak can be demonstrated without wraparound**.** Doppler waveforms with aliasing

will result in inaccurate peak systolic measurements unless the aliased and nonaliased signal velocities are manually added together (Figure2-19). (Table2-2) shows all the direct criteria for the detection of more than 60% (RAS).

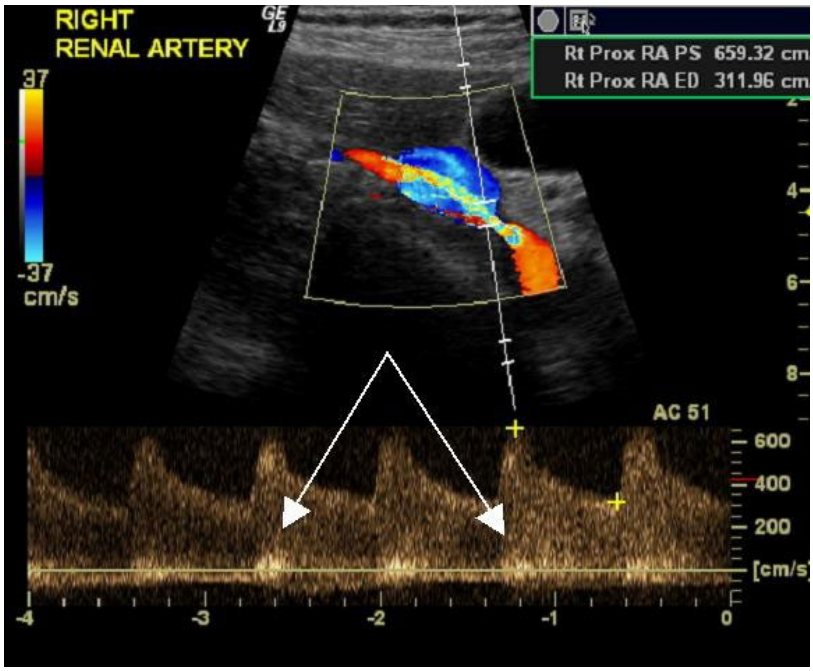
Even in the best hands, it is difficult to detect accessory renal arteries on all patients. This remains a pitfall with thus technique. Other limitations include over laying bowel gasses and patient obesity. In most instances, the renal arteries can still be evaluated in these cases by using the various windows described earlier. In obese patients the decubitus position is most often successful. The patient is asked to relax the abdomen this allowing it to rest on the table surface. The probe is positioned in the soft part of the adipose tissue just lateral to the midline. In this view, the abdominal aorta and origin of the renal arteries can be seen (Figure2-20).Scanning these patients from anterior approach usually results in failure because the beam must now penetrate the largest mass of adipose tissue. Furthermore, the patient typically resists the probe pressure by tensing their abdomen in this position. Another common problem is difficulty in obtaining a satisfactory Doppler angle. However, by using multiple approaches, it is usually possible to obtain an adequate angle of incidence.(Matthias,201)

Direct criteria for detection of RAS > 60%
1. PSV > 200 cm/sec
2. RAR > 3.5
3. Post-stenos is turbulence

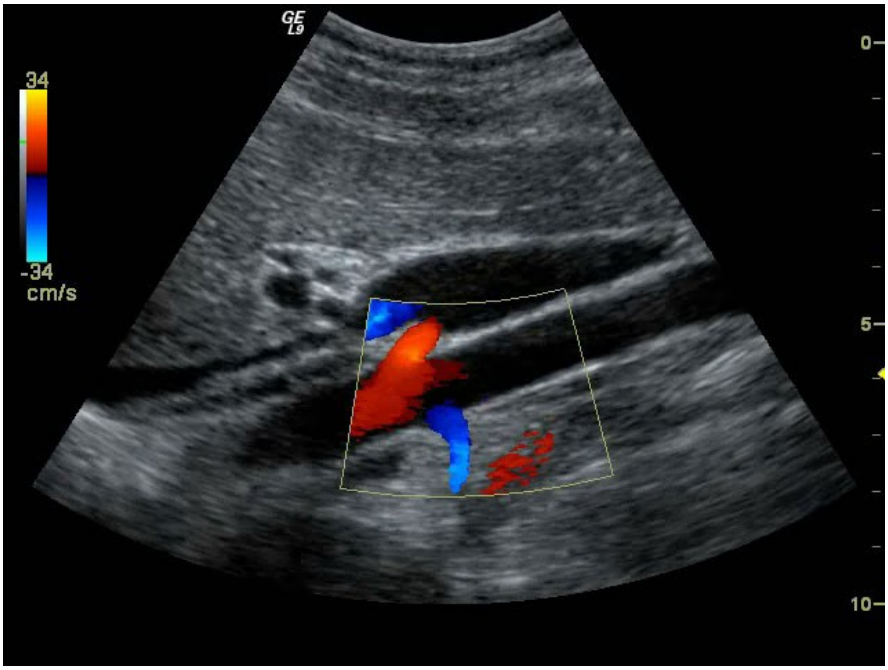
Table (2.2): Direct criteria for detection of (RAS) (WHO)



Figure(2.18) : renal aortic ratio (RAR) (Satish,2003)



Figure(2.19): Doppler ultrasound waveform with aliasing (Matthias,2001)



Figure(2.20): Abdominal aorta and the origin of the renal arteries (Matthias,2001)

(2.1.3.2): Indirect evaluation

The indirect evaluation of renal artery stenosis adds another layer of information to that already obtained from the direct method. By combining the two methods, a more accurate exam can be obtained. Indirect evaluation involves Doppler interrogation of the segmental or interlobar arteries within the kidney. A complete exam includes evaluation of the upper, mid and lower pole segmental arteries. If a steno tic accessory artery is feeding one of the renal poles, an abnormal waveform will be detected in that segment. This helps to compensate for any missed accessory renal arteries with the direct method.

Color or power Doppler is essential in identifying the intra renal vessels and determining an optimal angle of incidence. High grade stenosis of a feeding artery, delays the systolic rise in arteries immediately distal to it. The resulting waveform shape is termed tardus parvus. Normal intra renal segmental and interlobar arteries display an early systolic peak (ESP) or notch at the beginning of systole. The (ESP) is absent with stenos is of the main renal artery exceeding 60%. The systolic acceleration time (AT) is measured from start of the systolic upstroke to the first peak or (ESP) (Figure2-21).Systolic acceleration times greater than 0.07 second are consistent with a main renal artery stenosis exceeding 60%. The (RI) is measured and compared between kidneys. A difference in (RI) between the ipsilateral and contra lateral kidney increases suspicion for renal artery stenos is on the side with the lower (RI). This difference is significant when it exceeds (-5). Other parameters that have been recommended include acceleration index (AI). The indirect method rely most heavily on patterns recognition (presence of ESP, tandus and parvus waveforms), AT and RI (Figure2-22) (Table 2-3).

Indirect criteria for detection of > 60% RAS:
● Absence of ESP.
● AT > 0.7 seconds.
● Tandus parvus waveform.
● (RI) difference between kidneys exceeding (-5).

Table (2.3): Indirect evaluation of (RAS) (WHO)

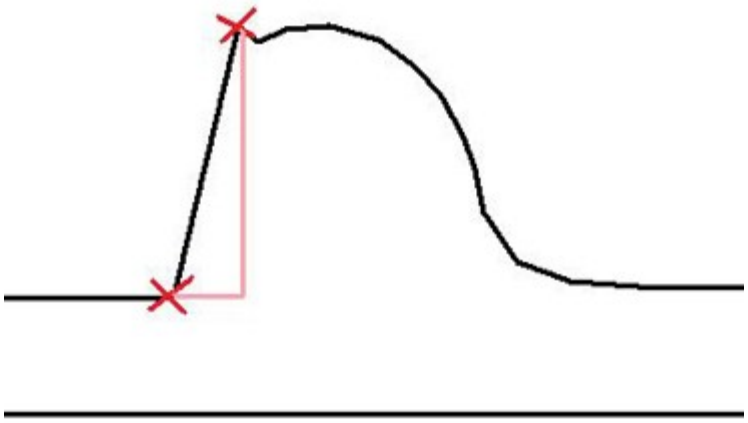
Attention to technique is crucial in performing thus examination. The study is best performed with the patient in a decubitus or oblique position. The scan plane is through the posterior axillary line. This results in a shorter Doppler distance and a better Doppler angle to the intra renal vessels (Figure2-23). It is very important to adjust the scan position in order to achieve a Doppler angle of incidence that is between 0-30 degrees to each vessel interrogated. A Doppler angle greater that 30 degree may not allow demonstration of the (ESP). Colour Doppler delineates the vessel path so that an optimal angle can be obtained.

Adequate evaluation of the intra renal Doppler trace required large, strong, well defined spectral waveforms. The Doppler sweep speed is set so that the display shows only 2-3 seconds at a time. This will spread out each cardiac cycle so that its components are more easily seen and measured. The system PRF is adjusted so that the waveform fills the entire spectral window. A higher frequency is used (3-5 MHZ0 compared to direct renal artery interrogation. This will produce a large frequency shift and correspondingly larger waveform, enhancing definition to the (ESP) and improving caliper placement for measurements.

High resistance within the intra renal arteries includes the sensitivity of the indirect technique. With high resistance, the (ESP) becomes exaggerated and may not

disappear with stenos is (Figure2-24). Likewise, it takes an even greater amount of stenos is before the acceleration time becomes abnormal and a tardus parvus waveform develops. Steno sis may still be suspected on the base of waveform comparison between side and noting an (RI) difference between kidneys. However, it is best to rely on the direct interrogation of the renal arteries wherever the (RI) is greater than 0.70. Other limitations associated with indirect evaluation of (RAS) include the inability to differentiate between severe stenosis and occlusion of the main renal artery. Collateral flow to the kidney in renal artery occlusion can produce an intra renal Doppler presentation similar to that seen with severe (RAS). Additionally, indirect Doppler evaluation is not sensitive to the detection of (RAS) less than 60%. Since renal artery stenosis of less than 60% is not thought to be hemodynamically significant and do not result in renovascular hypertension. This limitation may not be of greater significance.

It is important to emphasize that use of poor Doppler angles and low Doppler frequencies can result in non visualization of the (ESP). The (ESP) is best seen at Doppler angles less than 30 degree and Doppler frequencies of 3 MHZ or greater. It is necessary to obtain Doppler sampling at the upper mid and lower pole of the kidney; otherwise, renovascular hypertension due to steno sis of an accessory renal artery will be missed. Bilateral tardus parvus waveforms could potentially be the result of a proximal steno sis in the aorta or aortic aneurysm rather than bilateral (RAS). Direct interrogation of the renal arteries will help to determine if stenosis is present. Evaluation of the abdominal aorta should be performed to rule out aneurysm.(Matthias,2001)



Figure(2.21): Measurement of systolic acceleration time

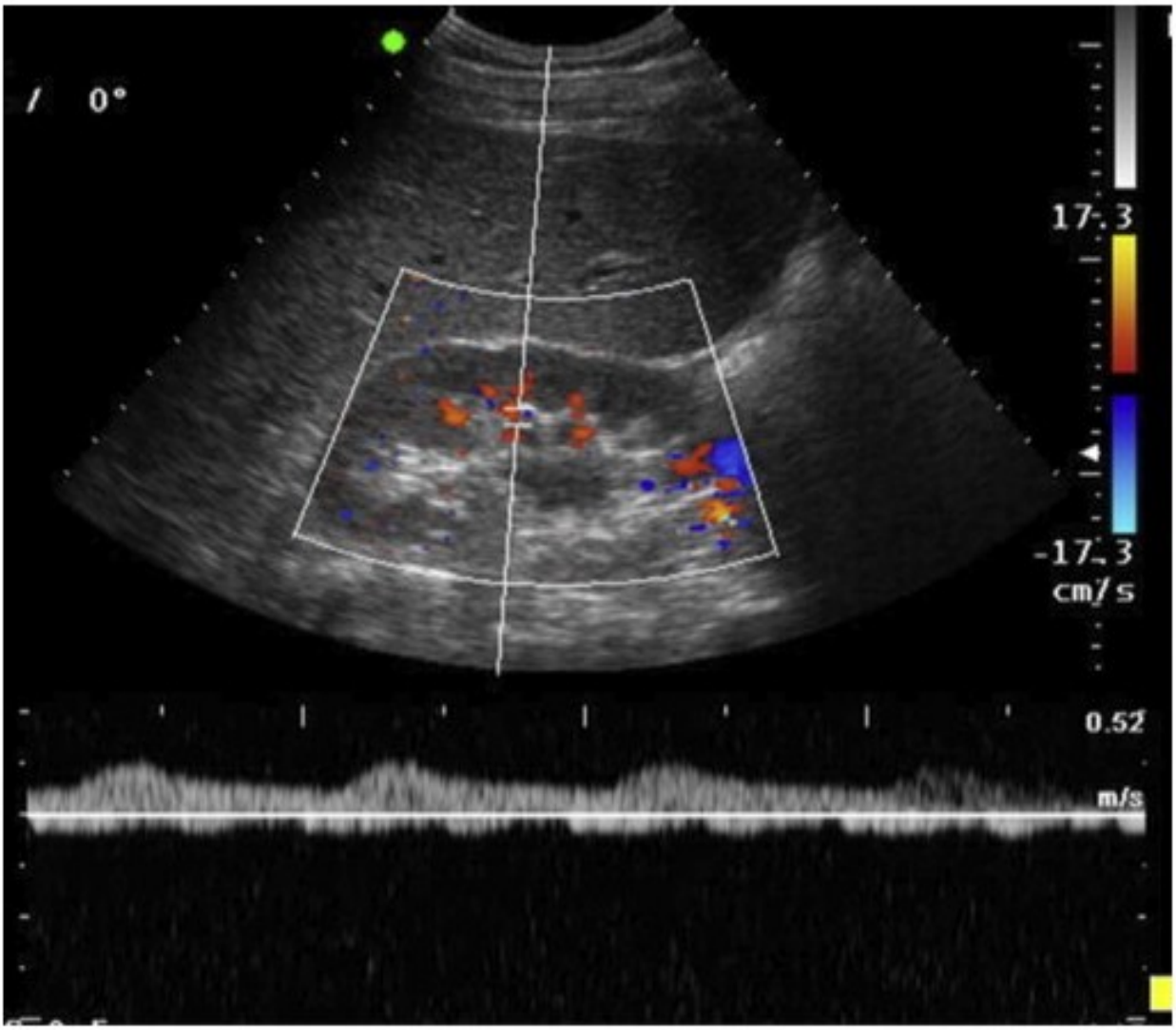
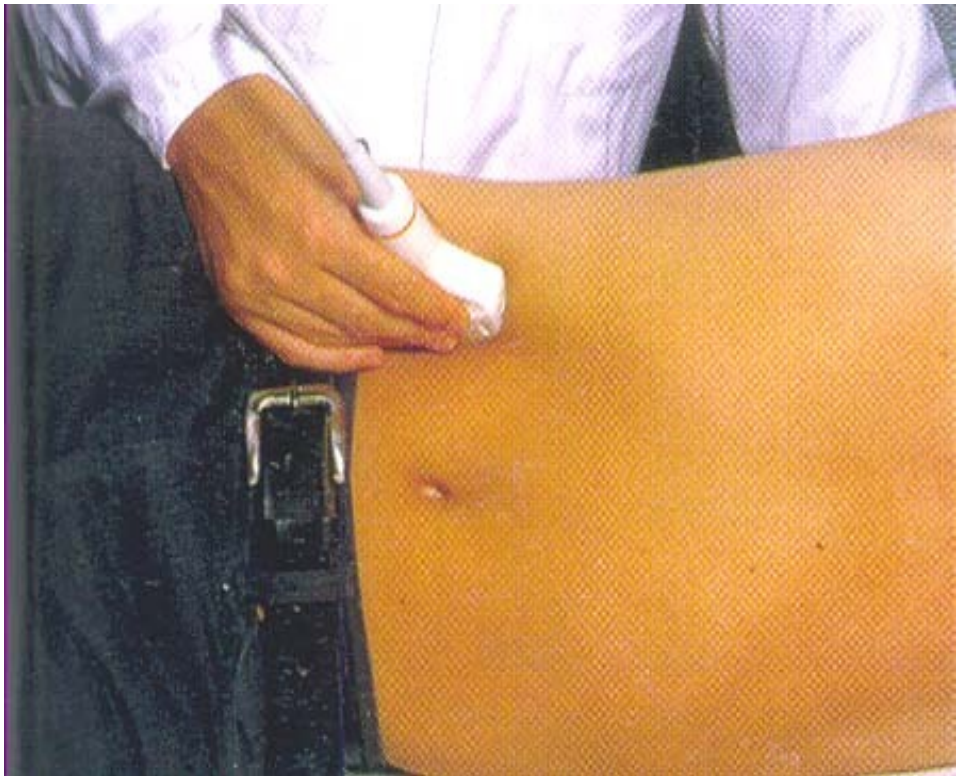
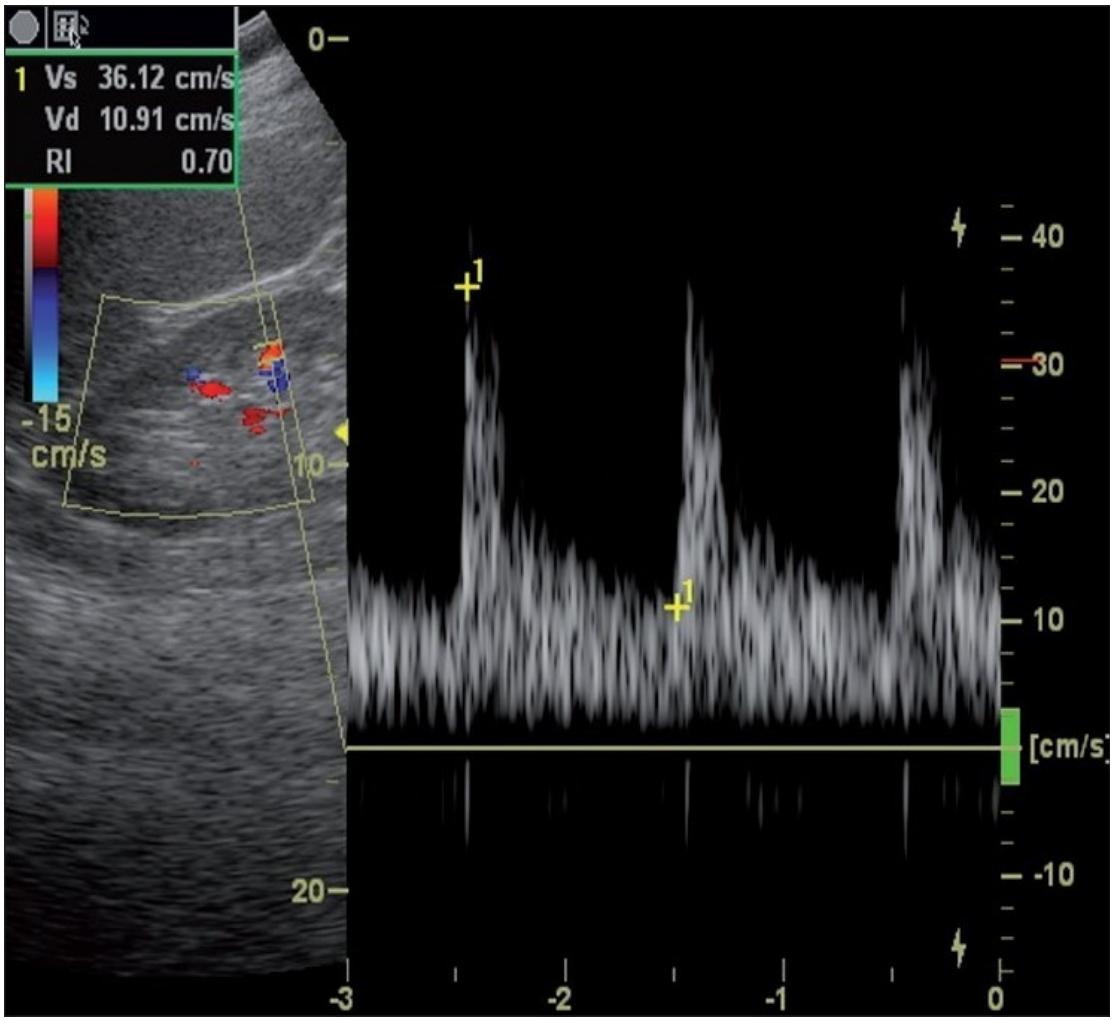


Fig. 7. Tardus–parvus waveform in a patient with RA stenosis. Note the delayed and dampened upstroke yielding a roun
appearance to the waveform.

Figure(2.22): Tardus parvus waveform (Hun,2000)



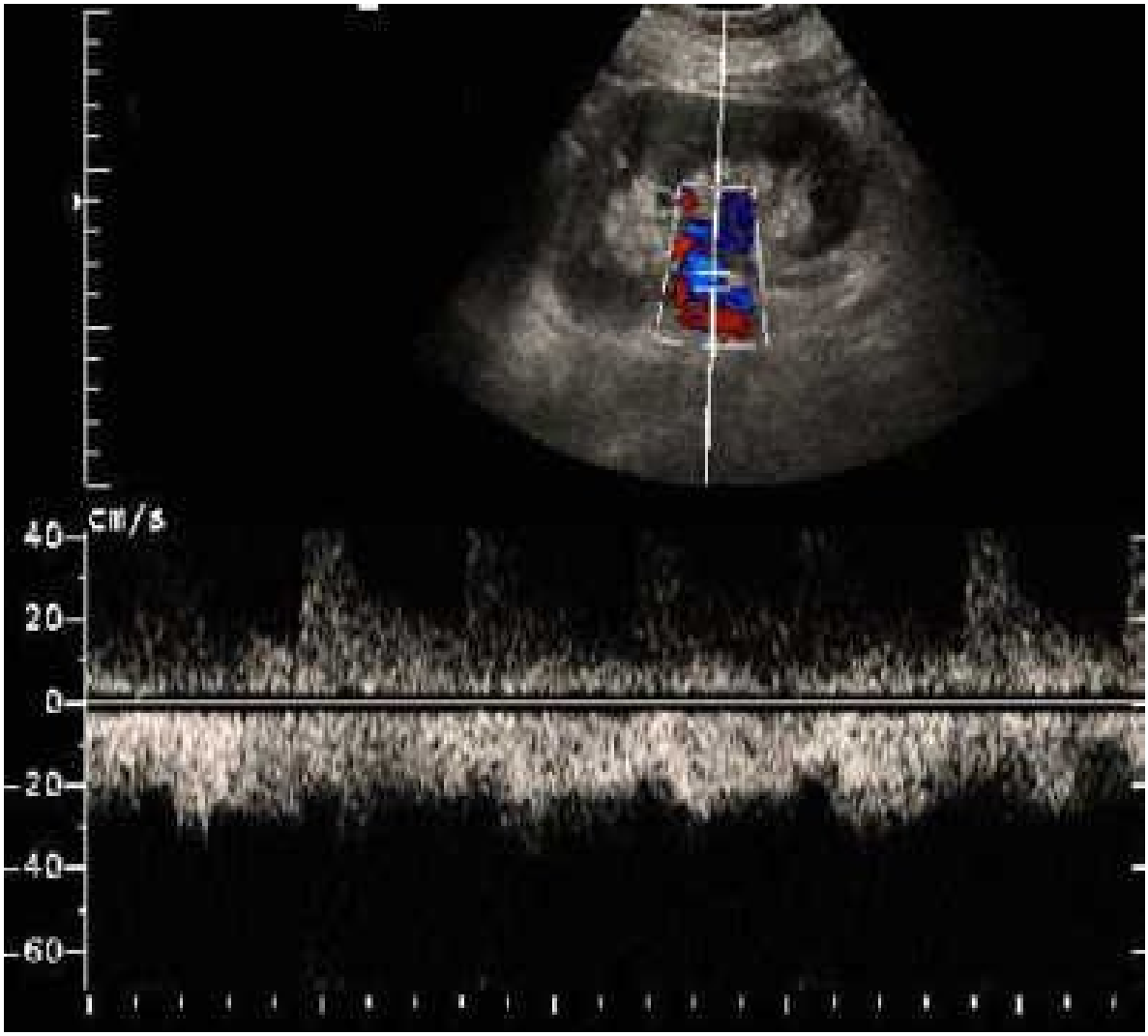
Figure(2.23): Dicubitus position for intra renal vessels (Matthias,2001)



Figure(2.24): High resistance intrarenal arteries (Satish,2003)

(2.1.4): Ultrasound evaluation of renal vein thrombosis:

This is uncommon condition in adults; it occurs most commonly in association with the extension of a renal tumor. Rarely, extrinsic compression or hematological conditions which produce an increased tendency to thrombosis may predispose to renal vein thrombosis. In infants, renal vein thrombosis may occur as a complication of dehydration. Colour Doppler may show no flow in the renal parenchyma or “flash flow” where the colour signal is seen only transiently, corresponding to peak systole. Occasionally a (to and fro) patterns may be seen with altering red and blue color signals visible within the renal arteries. Spectral Doppler may show absent or reversed, diastolic flow (figure2.25) . A (W) shaped to the arterial diastolic flow component, in association with absent venous flow on color Doppler is thought to be characteristic of renal vein thrombosis although other conditions may produce reversed diastolic flow, including acute tubular necrosis and cardiac abnormalities such as aortic incompetence. (Paul,2000|)



Figure(2.25): Doppler ultrasound for renal vein thrombosis (Paul,2000)

(2.2) Previous Studies:

Many studies were published regarding ultrasound measurement for kidney size worldwide. Some countries have already established their normal renal length and volume. These studies were conducted to provide reference values for renal size so as to differentiate between normal and abnormal kidneys early and quickly by using ultrasound. Most of these studies were conducted in low attitude areas such as Pakistan, Indian, Denmark, South Africa and so forth. Few studies were done to investigate the renal size by ultrasonography in high attitude area. The combination of all results from wide scale and dedicated surveys give a comprehensive guidance levels for renal size. Therefore these data could be important to diagnose the problem in kidneys easy and to give the patient the suitable treatment in a short time.

A recent study by Syed Athen et al. in their work entitle “Sonographic measurement of renal dimensions in adults: a survey to established age and sex based diagnostic reference values in Pakistan. The study assessed the normal range of values for renal dimensions in a symptomatic adult population with various age groups. The mean kindly lengths were 9.7 cm on right side and 10 cm on the left. The mean width was 4.6 cm, centical size was 1.46 cm with estimated average kidney volume was 35.7 cm^3 (Syed, 2012).

A study by Brandt TD et al. (ultrasound assessment of normal renal dimensions) in, (Chicago), confirms the accuracy and reliability of sonographic assessment of renal size. They showed that sonographic dimensions are smaller than those obtained by radiology. With the improve position, the mean renal length was found to be 10.7 cm in the right side and 11.1 cm in the left. (Brandth, 1982)

Study by Emamian et al. was performed on 665 adult volunteers using renal sonography. It showed a median renal length 11.2 cm on the left side and 10.9 cm on the right side. The median renal volume was 146 cm^3 in the left and 136 cm^3 in the right. Renal size was found to be decreased with age increased due to parachymal reduction. (Emamian, 1992)

Berhard Glodny in their study (Normal kidney size and its influencing factors) were applied normal ultrasound values for pole-to-pole kidney length. Cortical size was also recorded. The length was 10.8 cm for the right and 11.13 for the left kidney. The cortical size was same in the right and in the left (6.6 mm). The most significant independent predictors for length and cortical size were body size, body mass index, age and gender. (Bernhard, 2009).

Mujahid Raza et al. in their study (ultrasonographic assessment of renal size and volume and its correlations with BMI in adults) assessed renal size by ultrasound in 4,035 adult subjects without renal diseases. Mean renal length on the right side was 10.16 cm, width was 4.2 amd thickness was 4.4 cm. On the left side, the length was 10.27 cm, width was 4.4 cm. On the left side, the length was 10.27 cm, width was 4.7 cm and 5.1 cm for the thickness. The mean renal volume on the right was 99.8 cm^3 and 124 cm^3 on the left. The study concluded that the volume in the left side was significantly larger the right in both gender. (Mujahid, 2011).

Renal volume was obtained by three dimensional sonographic transducer with matrix arrays by Hyun Cheol Kin et al. One hundred normal populations were enrolled in this study. Two dimension and three dimension techniques were performed to the sample size to calculate renal volume. Volumes determined by three dimensions were found to be same as conventional two dimensional volumes. (Hyun, 2008)

Adeela Arooj et al in their study (comparison of renal size among different ethnicities), were used two dimensional ultrasound machine for one hundred university students to assess the renal size. Before starting the exam, height and weight was taken. The image was taken in supine position. The mean length for the right and left were 9.7 cm and 9.9 cm respectively. The mean width was 5.6 cm and 6.07 for the right and left respectively. (Adeella, 2011).

In Sudan, no studies was found to describe the renal volume by ultrasongraphy.
In high attitude areas, there were very few studies have been conducted to evaluate the normal renal size.

Ray B et al in their work entitled “Renal dimensions in Nepalese population a primary study: a survey to established normal values was conducted by using ultrasound. Right kidney was 9.1 cm long, 5.3 cm wide and 3.8 cm thick. Left kidney was 9.1cm long, 5.3cm wide and 3.8cm thick. Kidneys were found to be shorter than people living in other part of the world. (Ray B, 2004). See (Appendix V).

Renal size and volume was also calculated in patients complaining of systemic diseases like hypertension. Adedeji A et al. evaluate the renal volume in hypertensive patients by using ultrasound. The volume was correlated with age, sex and body mass index (BMI). Renal volume was calculated from kidney length, width and thickness using ellipsoid formula. The range of renal volume obtained was (51.6 – 205 cm^3) with a mean of 114cm^3 for the left kidney and (47.37 – 177.5 cm^3) with a mean of 10.6.14 cm^3 for the right kidney. The mean volume of right and left kidneys in male (112.9 and 123.11 cm^3 respectively) were significantly higher than in females (99.31 and 105.1 cm^3 respectively). (Adedeji A, 2010).

Sten Norby Rasmussen et al. correlated renal size to renal function and evaluate the transplanted kidney in relation to rejection in hypertensive patients. Ultrasound scan was performed through each kidney and volume was computed based on cross-sectional area. In 16 autopsy studies a high significant correlation between calculated and true values were obtained. (Rasmussen, 1998).

The effect and complication of hypoxia on kidneys were also evaluated by using Doppler Ultrasound in high attitude areas worldwide. The purpose of these studies is to assess the flow of blood in renal arteries and to measure the presence of atherosclosis.
A recently published study by Mazzali Marilda et al. were done on rats submitted to chronic hypoxia. Chronic hypoxia was induced in rats by placing them in a hypobanic champer for up to 24 days. Blood pressure and kidney biopsies were taken. Doppler ultrasound examination was done for renal artery. The study concluded that hypoxia was

associated with endothelial cell swelling in arteioles after 6 hours, followed by thickening of the arterioles, then tubulointerstitial injury and inflammation is occurred and it was progressive. A significant elevation in blood pressure was observed due to hypoxia. (Mazzali, 2003).

Gold Blott, suggested that the pathogenesis of hypertension of rats in previous study is due to primary disease of renal arterioles (atherosclerosis) and this can lead to renal ischemic and an increase in blood pressure (Blott, 2003).

Flemming et al. in German, used rats after they have been exposed to hypoxia. Doppler ultrasound examinations was done for kidneys. The study showed a decrease in renal haemodynamics (Flemming, 2000).

In order to demonstrate the effect of hypoxia on growth and development in high altitude area, Reza Farahani, et al. exposed postnatal 2 day nice up to 4 weeks and examined the effect of hypoxia on body and organ growth. The study concluded that there is a decrease in liver, kidney and brain size (Farahani, 2007).

To evaluate the flow of blood in renal arteries and to assess the degree of atherosclosis, Doppler ultrasound examination was performed. Many studies were published for this reasons by using different intra and extra renal Doppler parameters. Giulgan Derminpolst et al. reviewed Doppler sonogrpahic data for 55 patients in whom a diagnose of renal artery stenosis (RAS) had been confirmed by angiography. Intra renal Doppler

parameters, acceleration index and acceleration time was used. All these parameters were abnormal in 42 kidney (76%) and normal is 13 kidneys (2450. The study concluded that isolated used of intrarenal Doppler parameter may lead to false results. (Gulgun, 2003).

Lorenzo S. Malatino et al. used estrarenal and intrarenal Doppler parameters for diagnosis of renovascular hypertension. Renal aortic ration (RAR) and peak systolic velocity (PSV0 was calculated beside the acceleration index for the main renal artery. All extrarenal parameters can not be considered as absolute values. The study support the use of extrarenal parameters for non-invasive detection of (RAS). (Malatino, 1998).

MA Kliemer et al. used acceleration time, acceleration index, pulsitility and resistive index and waveform features in early system. The study concluded that, tendus-purvury waveform features in the distal renal artery is not an adequate screening method for detection of renal artery stenosis (MA kliemer, 1993).

Thiago A. et al. were use Doppler ultrasound to check the incidence of atherosclosis renal artery stenosis in hypertensive patients. 136 patients were enrolled in the study. RAS >50%, RAS <50% and no (RAS) had consecutively 13.2%, 14.7% and 72% of patients. The study concluded that the incidence of (RAS) was high. (Thiago, 2013).

R. Souza Deoliver et al described a new index, renal segmental ratio (RSR) for detection of renal artery stenosis. A total of 96 kidneys were studied with angiography and Colour

Doppler ultrasound independently. The Doppler parameters applied were peak cystetic velocity (PSV), renal aortic ratio (RAR), acceleration index (AI) and renal segmental ratio (RSR). The result indicate that (RSR) (95% sensitivity and 89% specificity) and (PSV) (83% sensitivity and 89 specificity) were the best parameters for (RAS) diagnosis. The results also show that Colour Doppler ultrasound is a reliable diagnostic modality for (RAS) diagnosis and the new indx (RSR) improves the effectiveness of the method. (Deoliver, 2000).

A prospective study was performed by GM Baxter, et al. in which Colour Doppler ultrasound was compared with angiography in 73 patients presenting for renal angiography. Colour Doppler ultrasound in 73 patients presenting for renal angiography. Colour Doppler ultrasound was unsuccessful in 16% of kidneys due to a combination of technical failure and small kidney size. No significant difference in intrarenal pulsitivity on resistive index was noted between the angiogrpahically stenosis and normal arteries. Acceleration time was found to be the best indication for (RAS). (Baxtery 1996).

Gabrielle J et al evaluated the test performance of duplex sonogrpahic parameters in screening for hemodynamically significant renal artery stenosis. Four parameters were evaluated: Peak systolic velocity (PSV), acceleration time, acceleration index and renal aortic ratio. (PSV) was found to have the greater accuracy than renal aortic ratio and acceleration index. Acceleration time versus acceleration index showed no evidence of difference in accuracy. The study concluded that (PSV) has the highest performance

characteristics, an expected sensitivity of 85% and specificity of 92%. The study also showed that additional measurement do not increase the accuracy. (Gabrielle J, 2007).

Chapter Three

Material and Methods

(3.1) Design of the study:

The study is case control study of analytical type in which abdominal ultrasound examination was done for hypertensive patients and normal population living in high altitude.

(3.2) Population of the study :

The target population for this research defined to include hypertensive patients with stage two hypertension and normal population living in high altitude. The hypertensive patients and the selective population should have several years of hypertension and living in high altitude therefore they will be in the best situation to furnish the researcher to see the effect of high altitude on kidney size and volume.

(3.3) : Study sample and type :

This study was a prospective study in which, a group of (175) hypertensive patients with stage two hypertension (systole ≥ 160 mm/Hg and diastole ≥ 100 mm/Hg) who lived in Aseer region was drown for ultrasound examination. Diabetic patients, patients with endocrine disorders, patients with aortic disease and patients with neurological disorders were excluded from the study. Gray scale and Doppler ultrasound exam was obtained for them by using different Doppler parameters to search for atherosclerotic renal artery stenosis. Another group of (325) healthy volunteers living in the same area are selected as a control group and gray scale ultrasound procedure was done for them. A sheet was designed for collection of data from the patients. This sheet include patient information ,

result of gray scale ultrasonography and the result of Doppler ultrasound (see appendix) . All patents were referred to ultrasound department by referring doctor for justified ultrasound procedure. The study was approved by Sudan University of science and technology and the clinic of ultrasound in King Khalid University. A verbal consent was obtained from all patients before undergoing the clinically requested ultrasound exam

. **(3.4): Area and Duration of the study:**

The study was take place is Aseer region, Abha, Kingdom of Saudi Arabia. This region is one of the thirteen administrative regions in the south western of Saudi Arabia. It was situated at 2200 m above the sea level. The highest point is in Al soda, 3200 meter above sea level. It is located between 40 and 42 longitude and 18 and 20 latitude. The climate of Abha is semi- arid and it is influence by cities high elevations. The temperature reaches 30° in summer and 5° in winter. The study started on May 2010 and finished on May 2012. (Buchele,2009). (Figure 3.1)


SYRIA
LEBANON
ISRAEL
Amman
JORDAN
Baghdad
IRAQ
Ar'ar
Sakakah
Tabuk
Duba
Ha'il
Buraydah
KUWAIT
Khafji
Jubail
Damman
Hofuf
Persian
Gulf
BAHRAIN
Doha
QATAR
Dubai
Abu Dhabi
U.A.E.
Gulf of
Oman
Muscat
IRAN
EGYPT
Red Sea
Medina
Yanbu
Riyadh
SAUDI ARABIA
Jeddah
Mecca
Taif
Abha
Jizan
SUDAN
OMAN
Khartoum
ERITREA
Asmara
Sana'a
YEMEN
Arabian Sea
Aden
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NORTH
0
250
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750
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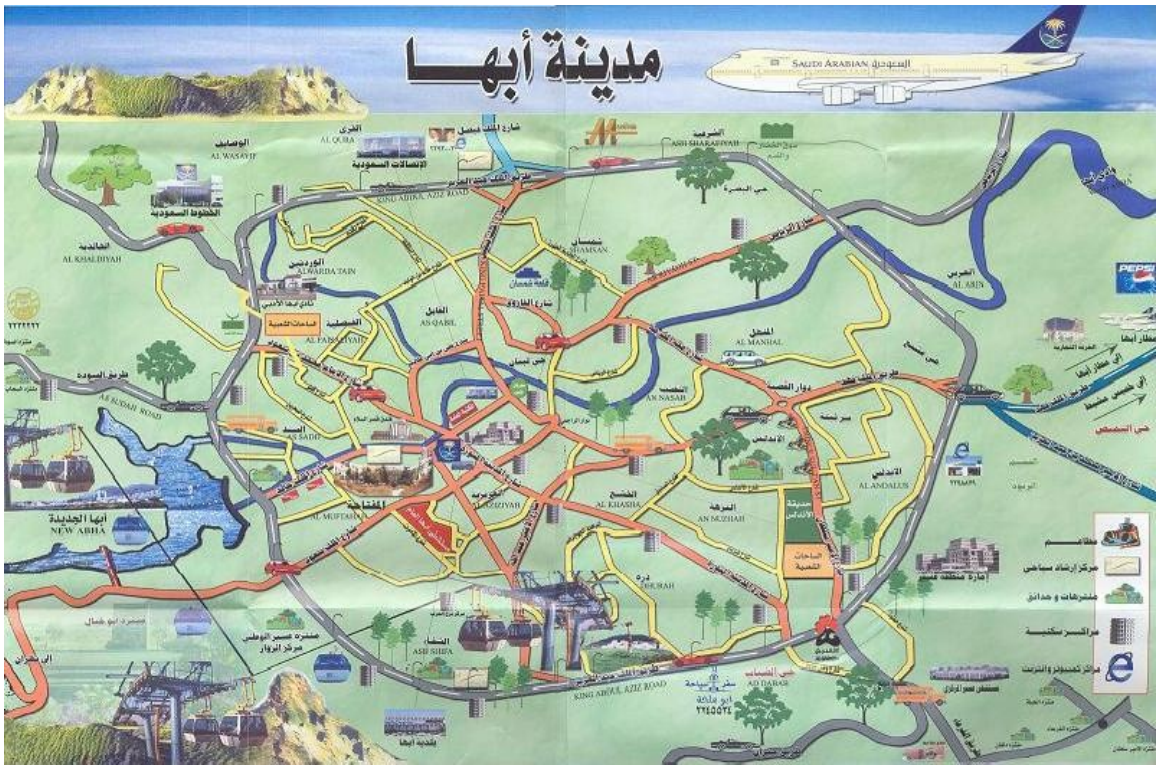
A



B

Figure (3.1): A: location of Abha in KSA map

B: Abha map.

(3.5): Equipment used in the study:

(3.5.1) **: Ultrasound machines:**

Three ultrasound machines, (logic 3) , LSD 3026WS5 , (logic book) and Philips C5-2/Abd vasc ware used in the study. The first two machines were belong to General Electric (GE) company, USA. The probes which were used in the study are curve linear multihertzs probes. Their frequency ranged from 2 up to 7 megahertz. Color flow imaging, pulse wave and power Doppler facilities were incorporate inside the machine. The machines have the ability to measure the volume of any organ under examination by obtaining the length, width and thickness. The machines also, have the ability to improve image resolution by using tissue harmonic imaging (THI). The screen in the first machine (logic3) was measured 15 inches and it was measured 10 inches in (logic book). For the purpose of recording the data, the machines have two printers, color printer and black and white printer (B/W). High density thermal papers ware used in the (B/W) printer and photographic papers were used in the color printer. There was also an archiving system inside the machines for storing the data. The machines also have the ability to make frozen image during scanning in gray scale and Doppler ultrasound. An ultrasound gel was used and it was putted at the top of the transducer to avoid reflection of ultrasound and to maintain a good transmission of ultrasound beam inside the body (Figure3.2).

(3.5.2) **: Other equipments:**

Standiometer was used for height measurement graduated in cm. Salter scale was used for the purpose of weight measurement and it was graduated in kg. Manual sphignomanometer was used for blood pressure (BP) reading. (Figure3.3)

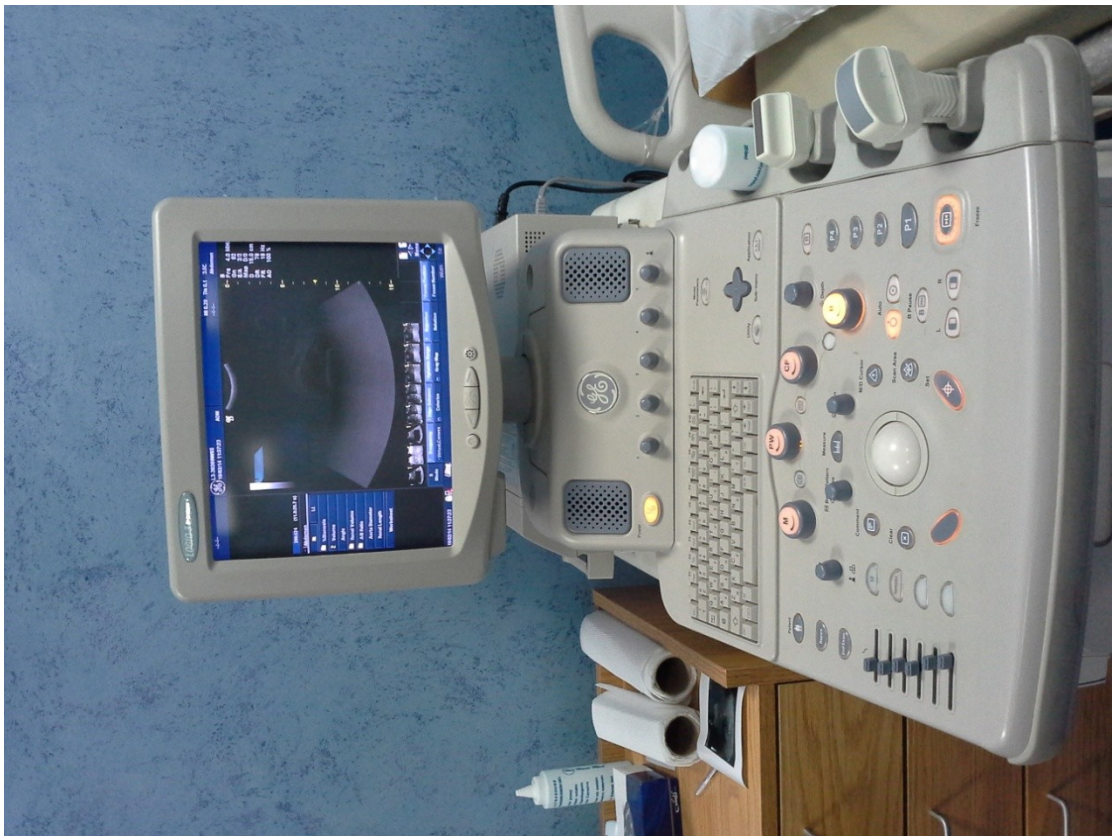
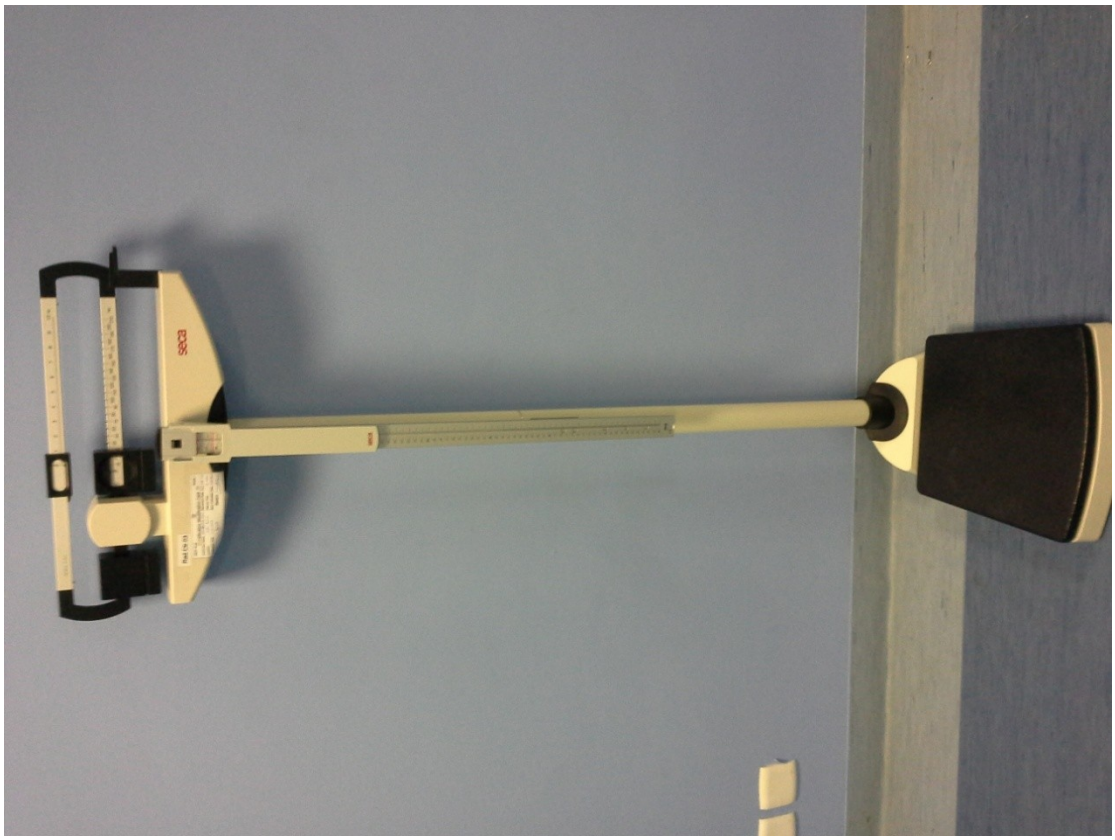


Figure (3.2) : Logic 3 General Electric ultrasound machine



Figure(3.3) : Height and weight measurement

(3.6): Technique and Protocol of the study:

(3.6.1)**: anthropometric measurement.**

Height was measured for each patient to the nearest 0.1cm using a height measuring board (standiometer) .The head positioned in horizontal plane , heals together and arms hang free . Weight was also measured using Salter,s scale graduated in

kilograms. Then body mass index (BMI) was calculated for each patient using metric system.

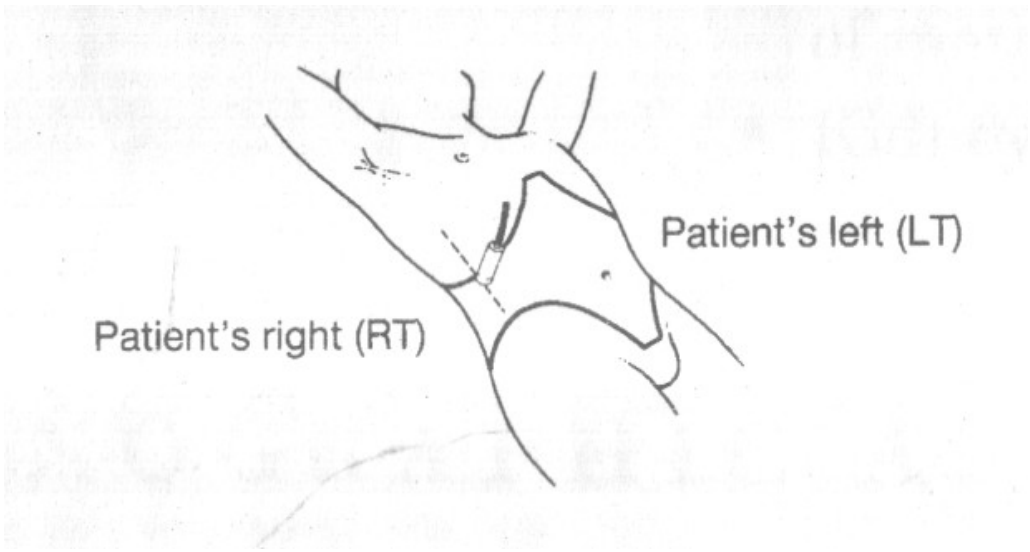
(3.6.2)**: blood pressure measurement.**

The blood pressure (BP) was measured by using manual sphygmomanometer. Patients firstly should have three to five minutes rest in quite environment before starting to read the (BP). This is to avoid any vasoconstriction due to stress or anxiety. Then (BP) was measured in sitting position with the arm supported at shoulder level .

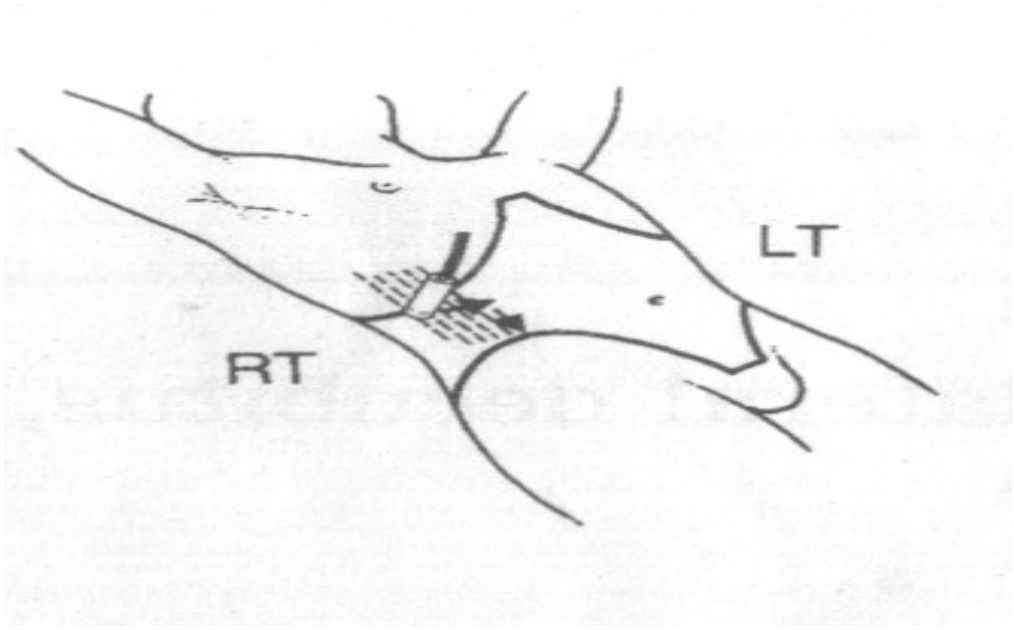
(3.6.3)**: gray scale ultrasound examination:**

For the purpose of decreasing the gases in the abdomen the patient fasted overnight, 6 hours before the ultrasound examination. All the participants were asked to empty the urinary bladder before the examination. Real time gray scale ultrasound was performed with logic 3, LSD 30269WS5, General electric, USA system with 3.5 MHZ curvelinear transducer with a wide 7cm contact surface. The examinations began with the subject supine. The para aortic region was examined to exclude the presence of horse show kidneys. Length, width, thickness and cortical size of the kidneys were measured. The longitudinal dimensions of the kidney were measured in a section visually estimated to represent the longest longitudinal section. Both lower and upper poles were defined. If the long axis of the kidney cannot be obtained with the patient supine, coronal or sagittal view with the patient in decubitus position was obtained. The patient asked to elevate the ipsilateral arm above the head and take a deep breath in order to have a good view for both poles. Supero inferior (pole to pole) measurement was taken in this view (Figure 3.4) . Then the width and thickness were measured in a section perpendicular to the long axis of the kidney as assessed from the longitudinal image. The probe was thus not

necessarily perpendicular to the skin. The level of this transverse section was intended to be placed quite close to the hilum of the kidney but at the same time free of pelvis (Figure3.5). Width and thickness were then measured in two orthogonal directions. Renal volume was estimated from the three orthogonal measurements on the base of ellipsoid formula. The size of renal cortex was also measured for each kidney in millimeters. The echogenicity of the cortex for each kidney was compared with the echogenicity of the liver in the right side and spleen in the left side to detect corticomedullary differentiation. The countor of each kidney was also observed. (Figure 3.6)

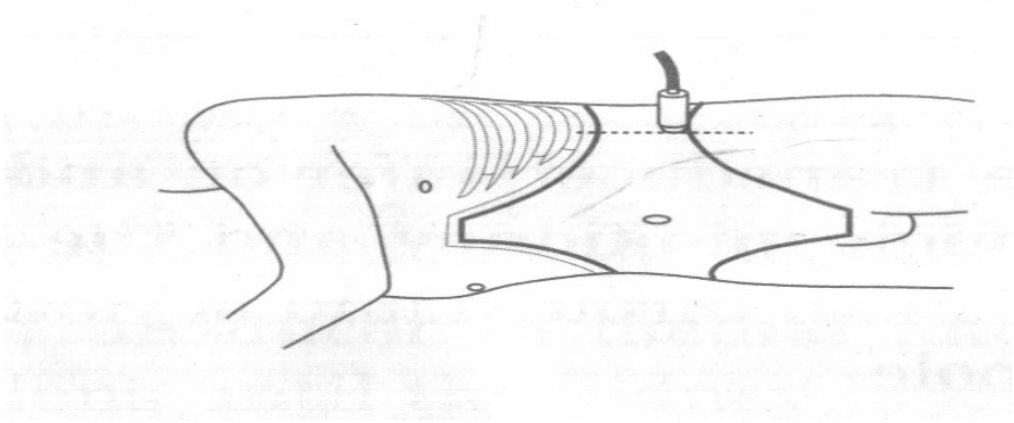


A

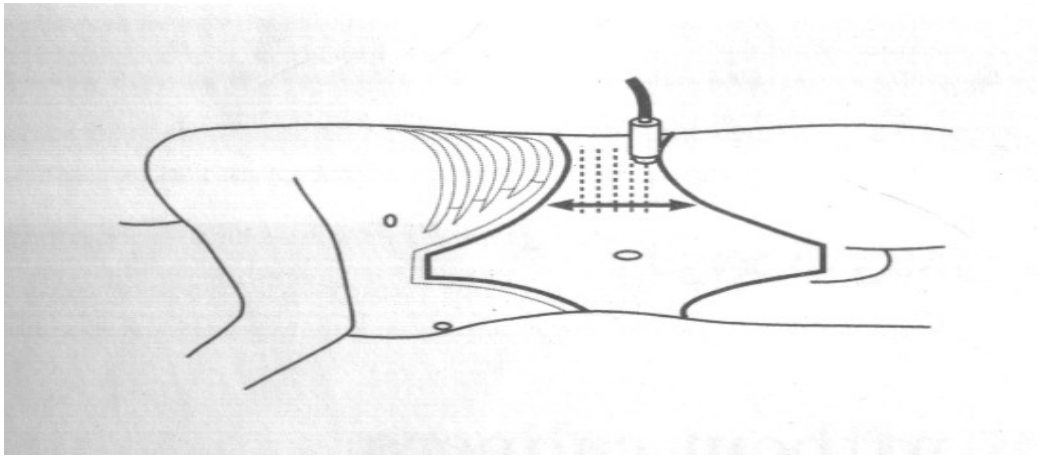


B

Figure(3.4): A and B longitudinal scan for the right kidney



A



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Figure(3.5) : A and B transverse scan for the left kidney

(3.6.4)**: Doppler ultrasound examination:**

Doppler ultrasound examination for renal artery for each kidney was carried out after good gray scale image. Color flow imaging (CFI) was applied for each kidney to see the flow of blood in renal arteries. Then pulse wave system (PW) was pressed and all the Doppler parameters was adjusted including angle correction and pulse repetition frequency (PRF), this is for accurate measurement of blood velocity in renal arteries. The walls of the renal were examined for atherosclerosis. Tracing of renal arteries was obtained starting from the origin near the aorta until the hilum of the kidney. Intrarenal vessels were also observed. Perfusion of each kidney was also observed by using color flow imaging or sometimes power Doppler imaging. The Doppler parameters which were used in this study include measurement of peak systolic velocity (PSV), resistive index (RI) and renal aortic ratio (RAR). These extra renal parameters were selected because they have high sensitivity and specifity as showed in chapter one. The site of measurement of these parameters was near the origin of renal arteries and near the hilum of the kidney . Any diameter reduction in renal arteries equal to or greater than 60% was considered as significant renal artery stenosis.

(3.7): Methods of data analysis:

The data were entered in Microsoft excel program and statistically analyzed by using SPSS (social package for statistical science) version 18. Descriptive and group statistics were used like mean, standard deviation and ranges. Correlation was made between the variables by using Anova test and independent sample T-test.

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Chapter Four

Results

This chapter describes results of gray scale and Doppler ultrasound for kidneys of patients living in high altitude. Ultrasound examination was performed for both kidneys and volume was calculated in order to measure renal changes for hypertensive patients living in high altitude. Renal arteries were assessed by using Doppler ultrasonography. The results were tabulated in forms of figures and tables depending on different variables used in the study. This chapter was divided in to three sections, general information including sex, age and body mass index, gray scale ultrasound results including kidney measurements and Doppler ultrasound results.

A total of 175 hypertensive patients, 95 males (54.28%) and 80 females (45.72%) were examined (Table4.1). The age range was 20 to 85 years with a mean of 59.93 years. The highest frequency of age (51.43%) was found above 60 years group and the lowest frequency (3.43%) was found in 20 to 30 years group in hypertensive patients (Table4.2). A total of 325 healthy volunteers described as a control group, 183 males (56%) and 142 females (44%) were also examined by using gray scale ultrasonography. The age of this group range from 23 to 70 years, with a mean of 49.92 years. Among the hypertensive patients, 90 (51.43%) were above 60 years old while there were only 52 (16%) in this group among the control (Table4.2).

Table4.1: Gender distribution in hypertensive and control group

Gender	Group			
	Hypertensive		Control	
	No.	%	No.	%
Male	95	54.28	183	56.00
Female	80	45.72	142	44.00
Total	175	100	325	100

Table(4.2) : Age Distribution in hypertensive and control group

Age	Hypertensive Group		Control Group	
	No.	%	No.	%
20 – 30	6	3.43	26	8.0
31 – 40	10	5.71	37	11.2
41 – 50	39	22.29	119	36.8
51 – 60	30	17.14	91	28.0
60	90	51.43	52	16%
Total	175	100	325	100

The body mass index (BMI), in hypertensive group range from 15.84 to 36.63 kg/m^2 while the BMI in control group range from 15.84 to 35.8 kg/m^2. In hypertensive group the mean BMI in female patients (22.47±5.16 kg/m^2) was higher than in male patients (21.27±5.58kg/m^2) but this difference was not statistically significant, (P = 0.14). In the control group, the mean BMI in males (25.13±4.26 kg/m^2) was higher than in females (23.78±3.59 kg/m^2), but this difference was also not significant(P = 0.35) (Table4.3).

Table 4. 3: Age and BMI distribution in hypertensive and control

Age	Gender	Hypertensive BMI	Control BMI
20 - 30	Male	32.27±1.24	32.49±1.78
	Female	32.27	-
31 – 40	Male	31.09±0.76	28.3±0.632
	Female	31.56±0.84	27.46±0.42
41 - 50	Male	28.02±1.23	25.86±0.55
	Female	27.42±1.5	25.79±0.57
51 - 60	Male	22.39±2.06	23.3±1.08
	Female	21.95±1.7	23.25±0.5
60	Male	17.34±1.07	17.7±0.80
	Female	17.48±1.05	17.28±0.71

The duration of hypertension was range between 10 month and 10 years with a mean of 2.42 years. More than half of the patients 97 (55.42%) have had hypertension for more

than 5 years,53 (30.29%) have had it for 1-5 years and 25 (14.29%) had it for less than one year (Table 4.4).

Table 4.4 : Duration of hypertension with gender

Year	Male	Female	Total
1	15	10	25 (14.29%)
1 – 5	26	27	53 (30.29%)
5	54	43	97 (55.42%)
Total	95	80	175

(4.1) : Gray scale ultrasound findings:

Regarding the result of gray scale ultrasound, the mean kidney length, width and thickness in hypertensive group for the right kidney were 9±0.4 cm, 4.9±0.4 and 3.4±0.5 respectively. The mean length, width and thickness for the left kidney were 9.5±6.2cm,4.9±0.4cm and 3.4±0.5cm respectively. In control group, the mean length width and thickness for the right kidney were 9.8±0.9 cm, 4.9±0.7 and 4±0.7 cm respectively while for the left kidney were 10.7±0.3 cm, 5.0±0.7cm and 4.3±.07cm respectively. The mean length of both kidneys in control group was higher than that in hypertensive group in both sides by 0.8cm in the right and 1.2cm in the left. The mean

cortical size for the right and left kidneys in control and hypertensive group was 1.8cm and 1.5cm respectively. (Table4.5).

Table 4.5*:* Average of kidney measurement in hypertension and control group

Kidney	Group	Length	Width	Thickness	Volume	Cortical size
Right	**Control**	9.8 ± 0.9	4.9 ± 0.7	4.0 ± 0.7	94.8 ± 23.1	1.8 ± 0.2
	hypertensive	9.0 ± 0.4	4.9 ± 0.4	3.4 ± 0.4	85.8 ± 17.3	1.5 ± 0.1
	P-value	0.000*	0.479	0.000*	0.000*	0.439
Left	**Control**	10.7 ± 7.3	5.0 ± 0.7	4.3 ± 0.7	106.6 ± 24.1	1.8 ± 0.2
	hypertensive	9.5 ± 6.2	4.9 ± 0.4	3.4 ± 0.5	82.9 ± 16.7	1.5 ± 0.2
	P-value	0.01*	0.039*	0.000*	0.000*	0.01*

Values are expressed as Mean ± SD; * Significant at P-value < 0.05.

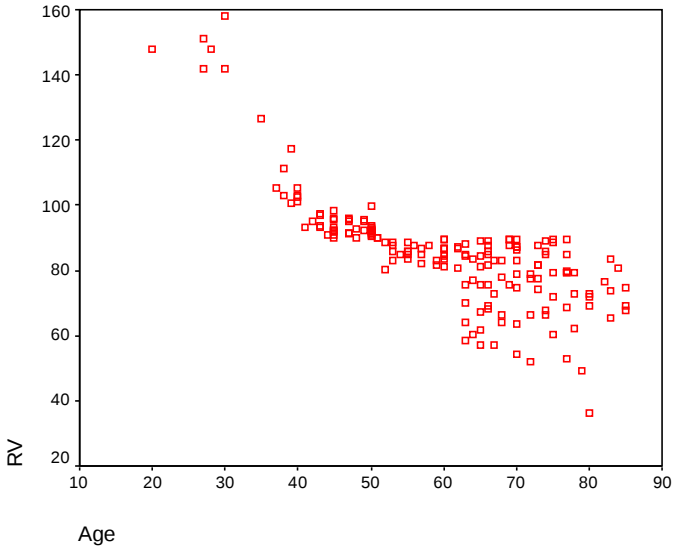
In hypertensive group, kidney volume range from 46.09 to 164.72 cm^3 for the left kidney and 36.28 to 158 cm^3 for the right kidney. In this group mean volumes of the right and left kidney in males (90.15±1.66 cm^3 and 87.36 ± 1.8 cm^3 respectively) were significantly greater (P = 0.00 and 0.02) than in females (80.32±1.9 cm^3 and 79.14±1.83 cm^3 respectively) (Table4.6). In the control group the range of renal volume was 57.46 cm^3 to 147.83 cm^3 for the left kidney and 57.10 to 147.78 cm^3 for the Rt kidney. In this group the mean renal volume for males on the left (87.4±1.93 cm^3) and on the right (88.06±7.47 cm^3) were greater than the mean renal volume in females (77.76±10.3 cm^3 and

76.10±12.4 cm^3 respectively), but the difference between gender was not significant (P = 0.20).

Table 4. 6: Age and volume distribution in hypertensive and control

Age	Gender	volume			
		Hypertensive		Control	
		Rt	Lt	Rt	Lt
20 - 30	Male	149.34±5.82	145.49±14.2	123.2±14.23	124.09±13.91
	Female	142.03	120.20	-	-
31 – 40	Male	111.75±12.93	117.13±7.60	97.7±1.99	98.40±1.99
	Female	105.89±6.25	102.89±4.75	92.86±1.32	93.19±1.22
41 - 50	Male	95.35±1.87	96.01±1.52	88.27±0.91	88.77±0.91
	Female	91.62±0.79	91.39±1.36	82.14±1.55	82.58±1.47
51 - 60	Male	87.85±1.94	89.22±0.51	78.16±1.02	78.64±1.06
	Female	84.40±2.28	85.18±1.06	72.29±1.61	72.67±1.56
60	Male	82.67±4.96	77.49±5.47	67.38±2.22	67.88±2.26
	Female	63.6±8.09	64.11±8.58	61.27±2.28	61.60±2.28
Total	Male	105.39±26.91	105.07±26.80	90.94±21.28	91.55±21.45
	Female	97.51±29.18	92.75±20.83	77.14±13.51	77.51±13.51

The largest mean renal volume from right and left kidney were recorded in age group 20-30 years in both gender, while the least mean renal volumes for right and left kidneys were recorded in age group older than 60 years in both gender. These was a significant negative correlation between age and renal volume with r = -0.83 and r = -0.9 ; P = 0.000 and 0.000 for right and left kidney respectively. The relationship of renal volume with age in hypertensive group shows that as the age increased renal volume decreased (Figure 4.1). It was also observed that left kidney volume was significantly larger than right kidney volume in each age group, r = 0.87, r = 0.90 with P = 0.01. In control group a negative correlation which was significant for both kidneys was also established between age and volume, r= -0.8 and -0.93, P = 0.0001 and 0.0001 for the left and right kidney respectively. It was also found that left kidney volume was also larger than right kidney for each age group in both genders see (figure 4.2).



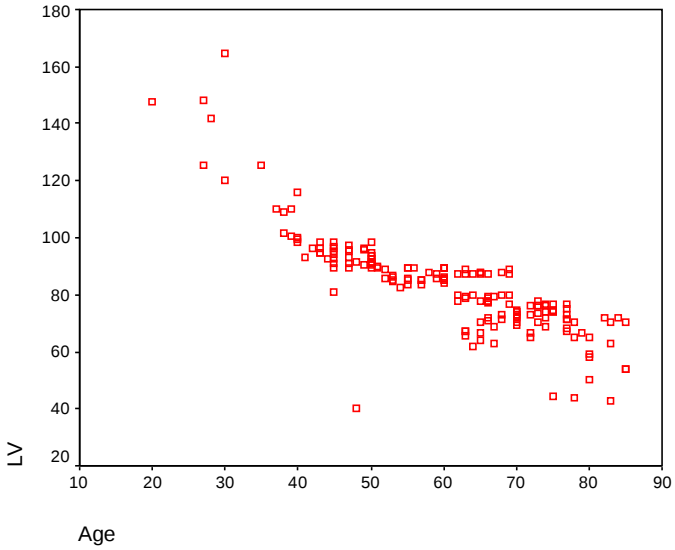


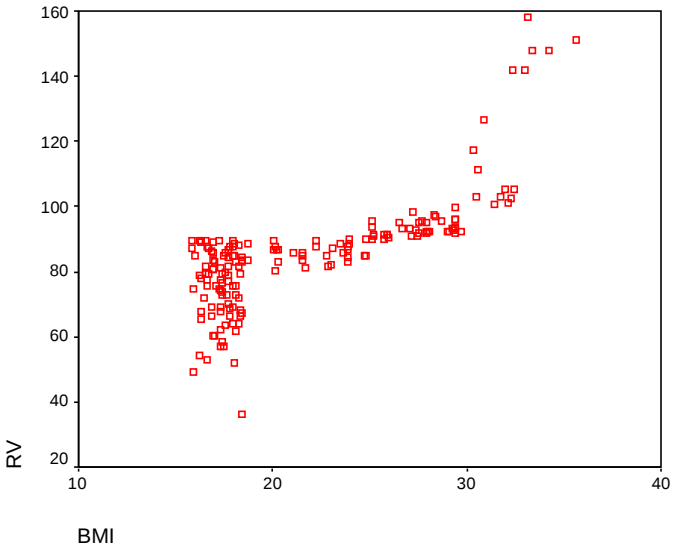
Figure 4.1 : scattered plot shows decreased in renal volume as the age increased in both sides (RV and LV).

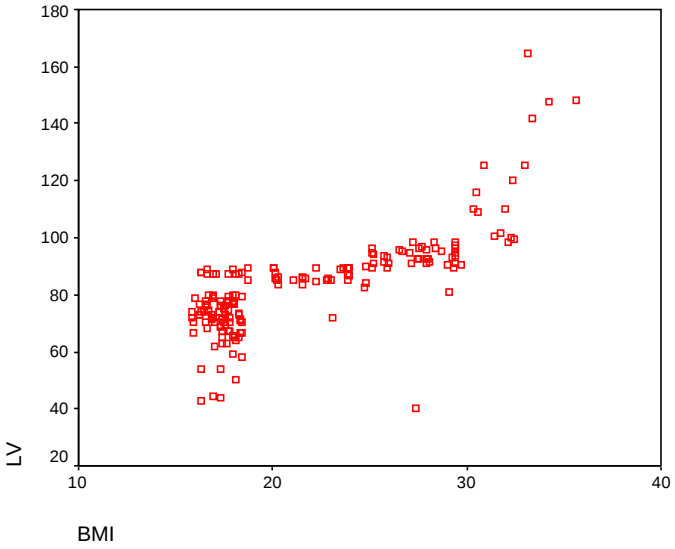
Figure (4.2) : correlation between RV and LV in control group

The distribution of BMI with mean renal volume in hypertensive group showed that the smallest mean renal volume was in the underweight group (BMI ≤ 20), while the maximum was in the obese group (BMI ≤ 30). Renal volume correlated significantly with BMI in hypertensive patients (r = 0.95 and 0.92; P = 0.000 for right and left kidney respectively) as well as in the control group r = 0.85 and 0.92, P = 0.000, respectively (Figure4.2) (Table4.7).

Table(4.7) : Renal volume of both kidney by BMI

BMI	volume					
	Hypertensive			Control		
	No.	Rt	Lt	No.	Rt	Lt
≤20	98	76.14±11.05	73.71±10.11	52	64.02±3.81	64.27±3.85
21 - 25	30	87.32±3.47	87.79±3.54	161	79.87±5.34	80.33±5.38
26 - 29	31	93.83±2.24	94.11±2.65	86	89.54±5.62	89.98±5.72
≥30	16	122.82±21.55	119.95±20.62	26	123.19±14.23	124.09±13.91





Figure(4.3) |: scattered plot shows relation between renal volume and BMI in both sides (RV and LV)

The volume was also correlated with kidney measurement (length, width and thickness) and it was found significant (P = 0.01, 0.03 and 0.000 respectively) in the right side, but in the left side the volume was correlated significantly with the width and thickness (P = 0.000 and 0.000) but there was no significant correlation with length (Table4.8).

Table4.8: Volume and kidney measurement in both sides

Correlations		Rt Length	Rt Width	Rt Thickness	Rt CT
Rt kidney	Correlation Coefficient	0.48	0.67	0.71	0.19
	P-value	0.000*	0.000*	0.000*	0.012*
Correlations		Lt Length	Lt Width	Lt Thickness	Lt CT
Lt kidney	Correlation Coefficient	0.05	0.62	0.77	0.27

	P-value	0.511	0.000*	0.000*	0.000*

* **Significant at P-value < 0.05.**

Gray scale U/S was also used to measure the cortical size and countor of the kidneys. The mean cortical size in the right and left was 1.5±0 cm, for the hypertensive group while it was 1.8±0.2 cm for the control group in both side. A significant correlation was found between renal volume and cortical size in both side (P = 0.01 and 0.000) (Table4.8). The countor of the kidney was also observed in both side, 140 (80%) hypertensive patients were found to have regular smooth counter and only 35 (20%) patients were have irregular counter. From the later group, 23 (65.71%) were complaining of renal artery stenosis (RAS) and the other 12 (34.29%) were hypertensive patients without (RAS). (table 4.9)

Corticomedullary differentiation was also recorded by gray scale U/S for both kidneys in hypertensive group only. 152 (86.86%) were found to have good corticomedullary differentiation and only 23 (13.14%) have poor corticomedullary differentiation, 11 (6.3%) in the right kidney , 8 (4.6%) in the left kidney and 4(2.2) in both side. (table4.10)

Table (4.9): Distribution of renal countor in hypertensive and control group

Countor	Group	Frequency	Percentage
regular	control	325	100%
	hypertensive	140	80%
irregular	control	0	0

	hypertensive	35	20%

Table 4.10 : Distribution of corticomedullary differentiation (CMD) in hypertensive group

CMD	Rt kidney		Lt kidney		Both side	
	frequency	%	frequency	%	frequency	%
Yes	11	6.3	8	4.6	4	2.29
No	160	91.4	163	93.14	152	86.86
Total	171	97.74	171	97.74	156	89.15

4.2: Doppler ultrasound findings

Doppler ultrasound examination was made to search for renal artery stenosis (RAS). From the total , 23 (13.14%) were found to have (RAS), 11 (6.3%) were in the right kidney, 8 (4.6%) were in the left and the remaining 4 (2.2%) were in both kidneys. The remaining group 152 (86.86%) were hypertensive patients without (RAS) see (table 4.11) . The mean length, width and thickness of the right kidney in patients complaining of (RAS) was (8.8), (4.3) and (3.2) cm respectively and it was (9.0), (4.3) and (3.3) cm in the left kidney respectively. The mean volume for (RAS) patients was decreased and it

was equal to57.02±8.11 in the right side and 55.35±9.2 in the left side. The mean cortical size in patients with (RAS) was different from the other group because it was found to be equal to 1.4cm in the right kidney and 1.3cm in the left kidney (table 4.12). A significant correlation was found between the length, width and thickness in (RAS) patients and length , width and thickness for patients without (RAS), (p= 0.000, 0.01, 0.000 in the Rt side and 0.01, 0.03 and 0.000 in the Lt). All the kidney measurements was decreased in (RAS) patients see (table4.12).

(RAS) was detected with the aid of three extra renal Doppler parameters, peak systolic velocity (PSV), resistive index (RI) and renal aortic ratio (RAR). The mean (PSV) for hypertensive patients without (RAS) at the proximal part of the main renal artery was found to be 98.7 m/s in the right side and 100.8 m/s in the left side. The same values was obtained at the distal part of the renal artery in both sides. But the (PSV) in patients complain of (RAS) was increased reaching 165m/s in the right side and 168 in the left side at the proximal and distal part of the renal artery . There was a significant difference (P=0.000) for (PSV) in the proximal and distal renal artery in the group of (RAS) patients and patients without (RAS) in both sides (table4.13). Regarding the resistive index, it was (0.6) in the right and left kidney for patients without (RAS) in both sites of measurement. But for (RAS) patients (RI) was increased reaching 0.8 in the right side and 0.9 in the left side at the proximal part of the renal artery . More increase was observed in the distal part of the renal artery reaching 0.83 in the right side and o.95 in the left side. Another significant difference (P=0.000) was found for (RI) in the proximal and distal renal artery in (RAS) patients and other hypertensive group in both sides (Table 4. 14).

(table 4.11): Frequency of (RAS) in right and left kidneys

RAS	Site
11 (6.3%)	**Rt**
8 (4.6%)	**Lt**
4 (2.2%)	**Bilateral**
23 (13.1%)	**Total**

Table (4.12)*:* Distribution of kidney measurement in (RAS) and Non-RAS hypertensive group

Kidney	Group	Length	Width	T	Volume	Cortical size
Left	**RAS**	9.0 ± 0.9	4.3 ± 0.7	3.2 ± 0.7	55.35 ± 9.2	1.3 ± 0.2
	Non- RAS	9.5 ±6.2	4.9 ± 0.4	3.4 ± 0.4	82.9 ± 16.7	1.5 ± 0.1
	P-value	0.000*	0.479	0.000*	0.000*	0.439
Right	**RAS**	8.8 ± 7.3	4.3 ± 0.7	3.2 ± 0.7	57.02 ± 8.11	1.4 ± 0.2
	Non-RAS	9 ± 0.4	4.9 ± 0.4	3.6 ± 0.5	85.8 ± 17.3	1.5 ± 0.2

	P-value	0.01*	0.039*	0.000*	0.000*	0.01*

Values are expressed as Mean ± SD; * Significant at P-value < 0.05.

Table(4.13) : Difference between (PSV) for (RAS) and non(RAS) patients in proximal and distal renal artery

RAS	**PSV /proximal**		**PSV/Distal**	
	Rt	**Lt**	**Rt**	**Lt**
Yes	165±25.9	168±14.9	165±25.9	168.5±14.9
No	98.7±22.3	100.8±21.1	98.7±22.3	100.8±21.1
P-value	0.000	0.001	0.000	0.000

Table(4.14) : Difference between (RI) for (RAS) and non(RAS) patients in proximal and distal renal artery

RAS	**RI /proximal**		**RI/Distal**	
	Rt	**Lt**	**Rt**	**Lt**
Yes	0.8±00	0.9±0.00	0.83±00	0.95±0.00
No	0.6±1	0.6±1	0.6±1	0.6±1
P-value	0.000	0.001	0.000	0.000

Renal aortic ratio was measured for all individuals and it was equal to less than 3.5 for all hypertensive patients without (RAS) in both sides and ranged from (3.5 to 3.9) for patients with (RAS)

The volume of both kidneys was correlated with the Doppler parameters (PSV and RI). Negative and significant correlation was observed for both parameters in both sides (Table4.15)

A significant correlation (p= 0.000 and 0.001) was observed between the volume of (RAS) patients and the volume of patents without(RAS) in both sides. The volume for (RAS) patients was decreased in both sides. (table4.12). A correlation was also made between the countor of the kidney in (RAS) group and the countor in non(RAS) group and it was found to be significant(r= -0.65 p=0.000). All patients with (RAS) (100%) was found to have irregular countor,while only (21.4%) of patient without (RAS) was found to have irregular countor see (table4.16)

Table (4.15) : correlation between volume and Doppler parameters

Correlations		Rt PSV	Rt RI
Rt Volume	Correlation Coefficient	-0.33	-0.30
	P-value	0.000*	0.000*
Correlations		Lt PSV	Lt RI
Lt Volume	Correlation Coefficient	-0.15	-0.21
	P-value	0.0051	0.005*

* Significant at P-value < 0.05.

Table 4.16: distribution of renal coutor and (RAS)

Contour		RAS	
		Yes	No
Regular	Count	0	140
	% percentage	0.0%	80%
Irregular	Count	23	12
	% percentage	100.0%	20%
Total	Count	23	152
	% percentage	100.0%	100.0%

Chapter five

Discussion, Conclusion and Recommendations

5.1 Discussion

Hypertension which is a major public health issue requires the heart to work harder than normal to circulate blood through the blood vessels. This will lead to many complications, like chronic kidney disease and impaired function of both kidneys. On the other hand kidneys hormonal response to narrowing in the renal artery will cause renovascular hypertension. The common cause of (RAS) is atherosclerosis specially in older patients. Many studies were conducted to show the prevalence of atherosclerotic

(RAS) in autopsies and rats, and in patients with coronary artery on peripheral artery disease. The progressive nature of atherosclerotic (RAS) has documented in several studies. The rate of progression has recently been classified by Duplex sonography. (Micheal,1998)

The normal size of a kidney is variable and affected by age, gender, body mass index and as well as the side. (see table 4.6 and 4.7). The size of a kidney provides a rough indication of renal function. Decrease of size and function are seen with chronic renal failure, renal artery stenosis and late stage of renal vein thrombosis. On the other hand, there is an increment in renal size in early stage renal thrombosis, early stage diabetes mellitus and renal inflammation. The number of nephrons in a kidney correlates with the physical dimensions and size of the organ. Hence there is need to have an accurate measurement of the kidney size, because the nephrons are the functional unit of the kidneys. The importance of accurate measurement of renal size cannot be over emphasized because recent studies have been suggested that the size of allograft on the ratio of the kidney weight to the dooner body weight, have the direct positive relationship to graft survival.(Elaine,2003)

Living at high altitude under hypoxic conditions has many effects on the kidneys. In the setting of polycythemia at altitude, studies showed a marked decrease in renal plasma flow (RPF) with a relative presentation of glomerular filtration rate (GFR) as consequence of an increased filtration fraction (FF). The increase in (FF) is caused by efferent arteriole vaso construction (Cymerman,2009). It was observed that a kidney at high altitude poses a risk of faster disease progression in those with pre-existing kidney disease. On the other hand, little evidence of injury or altered function was observed in

individuals living at high altitude without kidney disease. Subjects living at high altitude are also known to develop large glomeruli. The mechanism was uncertain, but could relate to the effects of low birth weight to cause low nephron number. High altitude populations are also suffer from hyperuricemia which was caused by hypoxemia and polycthemia. The higher prevalence of hyperuricemia associates with both the presence of microalbuminuria and hypertension(Reza,2007).

This study was conducted to determine renal volume in patients with hypertension living in high altitude by using ultrasoography. Measurement of renal volume was performed by ultrasound, because it has been regarded and preferred as an imaging technique of choice in most of the clinical surveys for being non-invasive, safe, reliable, cost effective and easy available. Although most studies have looked at kidney length, renal volume is better approximation of renal size than length measurement, because the shape of the kidney varied considerably. In addition, volume can also be valuable for evaluating possible compensatory hypertrophy, for correlating renal size to renal function and for evaluating the transplanted kidney in relation to rejection and its response to therapy.

This study collaborate the work done for normal subjects at sea level areas like Pakistan, Denmark and normal subjects in high altitude areas like Nepal and Ethiopia.

Regarding the hypertensive group it was also correlated with studies done in sea level areas like Nigeria (Adedeji,2010). The normal renal length in normoxic areas varied from 10 cm to 12 cm depending on ethnic background, age, side and sex. This study group showed decrease in renal length for normal populations and it was found at the lower scale of normal sea level population. The length of our study group was found to be greater than the length of kidneys of Nepalese population (7000m height), but

regarding the width, the Nepalese kidney was greater (Ray B,2004). This study showed that the kidney length in hypertension group was decreased from the normal and this decrease was observed also in low altitude area like Nigeria. More decrease was observed on our study group. This is due to the fact that organ size is related to the body size, so the smaller length of our study group is reflection of the relatively small body size as illustrated in (table 4.3). It may also due to the fact that, atherosclortic change in the kidney may affect the glomerular arterioles, resulting in ischemic changes in the glomeruli and post glomerular structures. Glomerular injury may also be a consequence of direct damage to the glomerular capillaries due to glomerular hypertension. The glomerular pathology progresses to glomerulosclrosis and eventually leads to atrophied kidneys. In addition to this, the rate of progression of atherosclerosis may be rapid in high attitude areas as approved in previous studies (Micheal,1998).

The mean renal volume we observed in the study for both control and hypertension group was decreased (see table4.5) from those volume reported in other studies at sea level (Brandt, 1982). This is possibly due to differences among ethnic group and also may be due to the fact that expose to chronic constant hypoxia may have different effect on growth and development in early life for some organs like kidneys and liver.

Though out the study, there was a marked and significant difference between the length and volume of the left and right kidney, with the left kidney larger than the right in both hypertensive and control group (as illustrated in table4.6). The enlargement of the left kidney in control group was great than hypertensive group. This difference has been reported by other investigators. The explanation of this is that, spleen is smaller than liver, so the left kidney has more space to grow and it is also found that the left renal

artery is shorter than the right, so increased blood flow in the left artery may result in relatively increase in volume.

As the age has an important bearing on kidney volume, it is found in our study that, the volume remains with marked decrease as the age increased till 50 years. After this age a rapid decreased in volume was recorded in both hypertensive and control group (see table4.6). This decrees in volume with age increased has been recorded by other investigators. The explanation of this is that the number of nephrons per normal kidney, which varies between 400,000 and 1,000,000 nephrons per kidney diminishes with increasing age. The shape of the kidney was also changed, it becomes wider and thicker with advance age, this is due to relaxation of abdominal wall, so that kidneys are less squeezed in older persons. (Snell,2004).

A significant positive correlation was also demonstrated between renal volume and body mass index (BMI), for both group in both sides see (figure 4.2), and this was reported in other studies (Mujahid,2011 and Zeb,2012). The cortical size in our study group for both hypertensive and control is greater than the cortical size in normoxic area(9.09mm in low altitude area and 1.5cm ,1.8cm in our study grouprepectivily). This variation is reflection of the fact that short kidneys with stocky infundibuli has thicker cortex than kidneys with enlongated spidery infundibuli (Adibi,2008)

The counter and conticomedullary differentiation are the most important parameters for detecting the progression of renal injury in hypertensive patients and in patients with

chronic kidney diseases living in a high altitude. These two parameters were received little attention in the literature (Krijnen,1998). The purpose of using these two parameters in our study is to find out progression rate and to know how far kidneys are affected by hypertension. In our study we find that all the hypertensive patients who have irregular countor and loss of corticomedullary differentiation were found to have hypertension caused by renal artery stenosis. This is possibly due to decreased in the perfusion pressure to a certain level which may lead to loss of renal parachymal mass and decreased glomerular filtration.

Probably because of difference in body size, renal volume have been found slightly larger in males in most of the studies (Syed, Brandt,Mujahid and Adeela). The same was observed in the current study, that showed a statistically significant larger kidney volume and cortical size in males (see table 4.6)

The duration of hypertension in the study was calculated from the time hypertension was first diagnosed in the hospital. It is difficult to determine the actual duration of hypertension because of the insidious on-set of the disease, which means that it can go undetected for a long time. There was no significant correlation between renal volume and duration of hypertension through most patients were in the group that have been diagnosed for more than 5 years (see table4.4). This is similar to findings in Nigeria but unlike other finding in Turkey, which showed that renal volume is smaller in hypertensive patients with chronic renal failure because renal volume decrease more in patients with chronic renal failure and hypertension (Adedeji,2010). This may show that hypertension affects renal volume when there is severe underlying renal parachymal damage.

Doppler ultrasound was made for hypertensive group to evaluate the presence of renal artery stenosis (RAS). The study collaborate the work done in normoxic area for hypertensive patients with and without (RAS).

The rate of (RAS) in patients with hypertension and diabetes mellitus is high, because they have higher prevalence of atheroschrotic vascular lesions. A study show that the prevalence of (RAS) is estimated to be between 2% (unselected hypertension) and 40% (patients with atherosclerosis) in low altitude areas. In our study the percentage of (RAS) among hypertensive group was found to be high (see table4.11). We feel that this is due to two reasons, firstly hypertension will increase the prevalence of atherosclerosis and this can be applied for low and high attitude area. Secondly, more progression of athersclorosis may be observed in high attitude area because of hypoxia. Due to lack of information, and variation of size between people living in high attitude, we were unable in this study to make comparison between the study group and other group living high altitude. Regarding prevalence of (RAS) among these population. So population based studies were needed for all high altitude areas to confirm our findings.

Previous studies in normoxic area (sten,1978,CD Thorn,1998)) show that the length and volume of both kidneys was decreased in patients complaining of (RAS). In the current study the volume in the group of (RAS) was decreased by (33%) as illustrated in (table4.11). This marked decrease was due to deficiency of blood flow to the kidneys, which may lead to atrophy and thus may be an important diagnostic clue for (RAS). It was also observed that a kidney at high altitude poses a risk of faster disease progression and altered function in those with pre-existing kidney disease. The study showed that the

majority of (RAS) patients are females with an average age of 74 years. The duration of hypertension for all (RAS) patients was greater than 5 years.

Doppler ultrasound for (RAS) is a multidirectional method that can vary in its accuracy, depending on parameters and indices and their location of measurement. It is still a matter of debate as to which parameters should be used for non-invasive diagnose of renovascular disease. All the previous studies suggested to use more than one parameter for accurate diagnose of (RAS), because single parameter can give us false results (Baxter,1996)|. The study used three – extrarenal parameters for detection of (RAS), because these parameters have the highest performance characteristics as it is approved and supported by many studies (Lorenzo,1998 and GM Baxter,1996). On the other hand, intrarenal parameters cannot be considered as absolute values because they lead to unacceptably high incidence of false-negative results and they also need an expert person (Gabrielle,2007).

Depending on the site of measurement, the value of the three extrarenal parameters, (PSV), (RI) and (RAR) which were used in the study for hypertensive patients without (RAS) were similar to those studies which were done in normoxic areas. For (RAS) patients, all the values of extrarenal parameters were increased reaching 168 m/s (PSV), 0.9 (RI) and 3.9 (RAR) and this is similar to previous studies in normal altitude areas. The increase in velocity parameters may be due to decrease in the lumen of the artery resulted from hypoxia. (see appendix IV)

(5.2) Conclusion:

Generally and regardless for altitude, normal values for kidney measurement are dependent on age, sex and body index. The result of this study provide valuable date for establishing reference values for kidney size in normal population and hypertensive patients living in high altitude by using ultrasonography. The study signifies the potential of ultrasound as a useful tool for diagnostic and follow up purposes of kidney disease. The data presented in this work showed that our renal size and volume were lower by approximately up to one third lower compared to the mean values presented in the literature for low altitude. In agreement with published studies, our study showed that

renal volume is higher in the left than in the right kidney in hypertensive and control group for both sexes. The female patients have smaller kidney size compared to males in both group. The study also showed that volume of both kidneys decreases with age increase and positive correlation between the volume and body mass index was observed. Furthermore, there is no correlation between renal volume and duration of hypertension. Additional survey studies are necessary to improve the statistical information by including different high altitude areas.

Renal artery stenosis which can be mild or significant is relatively common finding among population with advance age and hypertension. Conventional ultrasound was limited because of the lackof functional and vascular information. Doppler ultrasound can reduce this limitations and it was done in our study to obtain the presence and direction of blood flow in the renal artery. In our study we use extrarenal parameters for the detection and assessment of (RAS), and (RAS) was detected in one seventh of the total study sample size. More decrease in the volume was observed for (RAS) patients in our study group in comparison to (RAS) patients living in normoxic area. To evaluate the progression of (RAS) and its effect to the kidneys, the counter and conticomedully differentiation in kidneys was observed. In our study, all patients with (RAS), were found to have irregular counter and loss of conticomedully differentiation in the affected side. The values of extrarenal parameters were increase and this is considered to be a diagnostic feature for (RAS). The selected site of measurement in our study for all extraneal parameter is in the proximal and distal renal arteries.

By extending this research and including data from other high altitude area, we can formulate normogram for kidney dimensions. Furthermore, reference table for kidney

size is extremely useful for routine evaluation and monitoring of kidney disease in people living in high altitude. We also feel that volume measurement can be useful for evaluation and comparison between the kidneys.

(5.3) Recommendation:

- When performing ultrasound, dependability of renal size on age, gender and body mass index has to be considered by the operator so as to differentiate between a pathological and a normal size small or large kidney.
- Regular ultrasound scanning for kidneys is recommended for hypertensive patients living in high altitude to avoid rapid atherosclerotic changes resulted from hypertension and hypoxia.

- The current clinical practice of using renal length measurement ultrasonophically can be improved on by volume measurement to provide accurate data for clinical and decision making.
- For every day situation, measurement of renal volume is therefore recommended.
- Furthermore, three dimensional (3D) ultrasound with a matrix array transducer is recommended to reduce renal volume measurement errors.
- this project measured renal volume in one area, so other high altitude area could be investigated for comparison depending on degree of altitude.
- More studies are needed to demonstrate the main cause of hypertension for populations living in high altitude.
- Measurement of renal volume for diabetic patients living in high altitude is also recommended to evaluate the effect of diabetes mellitus and hypoxia to kidneys.
- Other organs measurements, like liver and spleen in high altitude is also recommended to establish a reference table for organ measurement in these areas.
- Population survey studies using Doppler ultrasound are needed to demonstrate the percentage of (RAS) in high altitude areas.

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